University of Alberta

I. CHEMOSELECTIVE CATALYTIC HYDROGENATION OF α, β-UNSATURATED ALDEHYDES AND KETONES USING SOLUBLE COPPER(I) HYDRIDES

II. FREE RADICAL ALKYLATION OF TITANIUM(III) ALLYL AND PROPARGYL COMPLEXES.

by

Jianxin Chen ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Department of Chemistry

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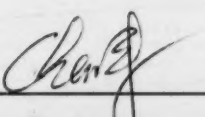

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To my parents and my wife, Wei Lin.

Abstract

The first part of the thesis pertains to the chemoselective catalytic hydrogenation of α,β-unsaturated aldehydes and ketones to allylic alcohols using phosphine stabilized Cu(I) hydrides. The investigation has determined that dimethylphenylphosphine and 1-phenylphospholane derived copper(I) hydride catalyst systems give excellent 1,2-selectivity for the reduction of α,β-unsaturated aldehydes and ketones, except in the case of some simple cyclic conjugated enones. Bidendate phosphines, trialkylphosphines and racemic dimethylbinaphthylphosphines do not generate selective and active copper(I) hydride catalysts. Interestingly, the racemic methylalkylphenylphosphine–derived catalyst series also gives good 1,2-selectivity and catalytic activity for most conjugated enal and enone substrates. More importantly, such chiral phosphine ligands can be made in nonracemic forms, and the chiral phosphines can potentially be used for future asymmetric copper(I) hydride catalyst research. The experimental results also demonstrate that catalyst selectivity and catalytic activity is very sensitive to the phosphine ligand structure; even a very small change in the phosphine ligand structure can dramatically change the catalytic reaction. In addition, changes in the reaction conditions, including the solvent, hydrogen pressure, phosphine concentration and *tert*-butanol co–solvent concentration, also affect the catalytic reaction. The investigation of the achiral and racemic ligands provides some basic data not only defining the ligand structure-catalyst activity relationship, but also for the development of asymmetric copper(I) hydride reduction catalysts.

The second part of the thesis describes an investigation of free radical alkylation of titanium(III) allyl and propargyl complexes. A new one–pot synthesis of titanacyclobutane complexes via Cp^*_2TiCl provides a very convenient method for the preparation of various β-substituted titanacyclobutane complexes. Continued research on the intramolecular free radical cyclization of titanium(III) propargyl complexes demonstrates that the full series of

bicyclic titanacyclobutene complexes with ring sizes from five to ten can all be made in high yield. Careful investigations of ancillary ligand effects find that the Cp* is not the only effective ligand for the free radical alkylation of titanium(III) propargyl complexes; the ^{t}BuCp, Cp, and 1,3–bis-TMSCp ligand sets also lead to the formation of titanacyclobutene complexes in good to excellent yields. More importantly, the investigation also shows that radical addition to these η^3-propargyl complexes is significantly facilitated by the use of stronger electron-donor ancillary ligands. The Cp* and bis-TMSCp ligand sets form titanacyclobutene complexes in high yield, while the less electron–rich ^{t}BuCp and Cp ancillary ligands lead to titanacyclobutene complexes in somewhat lower yield. Steric hindered ligands do not inhibit the radical addition reaction. An investigation of the functionallization of the titanacyclobutene complexes shows that only the Cp ligand derived titanacyclobutene complexes undergo facile ketone and isocyanide insertion reactions. Hydrolysis of the ketone insertion product generates useful organic molecules after demetallation.

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Table of Contents

page

I. PART ONE: CHEMOSELECTIVE CATALYTIC HYDROGENATION OF α, β–UNSATURATED ALDEHYDES AND KETONES USING SOLUBLE COPPER(I) HYDRIDES 1

A. Introduction and Historical Perspective 2

1. Chemoselective Catalytic Reduction of α,β-Unsaturated Carbonyl Compounds 2

2. Reduction of α,β-Unsaturated Carbonyl Compounds Using Cu(I) Hydrides 12

B. Project Goals 24

C. Results and Discussion 28

1. Catalytic Hydrogenation of α,β-Unsaturated Aldehydes and Ketones Using Me_2PPh–Stabilized Cu(I) Hydride and Hydrogen.

a. Investigation of the catalytic reaction conditions 28

b. 1,2-Reduction of α,β-unsaturated aldehydes and ketones 39

2. Investigation of The Chemoselectivity and Catalytic Activity of New Catalysts.

a. Bidendate phosphine catalysts 51

b. Common tertiary phosphine catalysts 56

c. Phenyl–substituted cyclic phosphine catalysts 58

d. Racemic alkylmethylphenylphosphine catalysts 63

e. Racemic binaphthyldimethylphosphine catalysts 69

D. Conclusions 74

II. PART TWO: FREE RADICAL ALKYLATION OF TITANIUM(III) ALLYL AND PROPARGYL COMPLEXES..... 76

A. Introduction and Historical Perspective..... 77

1. Free Radical Addition Reactions of Transition Metal Allyl Complexes..... 77

2. Free Radical Alkylation of Transition Metal Propargyl Complexes..... 91

B. Project Goals..... 104

C. Results and Discussion..... 108

1. An Improved Method For The Synthesis of Titanocyclobutane Complexes

a. Introduction..... 109

b. One pot synthesis of titanacyclobutane complexes using Cp^*_2TiCl..... 111

2. Intramolecular Free Radical Cyclizations of Titanium(III) Allyl and Propargyl Complexes

a. Introduction..... 114

b. Intramolecular free radical cyclization of Ti(III) allyl complexes..... 118

c. Intramolecular free radical cyclization of Ti(III) propargyl complexes..... 121

3. Radical Additions of Titanium(III) Propargyl Complexes Using Cp and ^{t}BuCp Templates.

a. Investigation of ^{t}BuCp templates..... 134

b. Investigation of Cp templates..... 139

c. Functionallization of titanacyclobutenes..... 147

D. Conclusions..... 155

III. EXPERIMENTAL

General..... 157

Part one. Chemoselective Catalytic Hydrogenation of α,β-Unsaturated Aldehydes and Ketones Using Soluble Copper(I) Hydrides.

A. Catalytic Hydrogenation of α,β-unsaturated Aldehydes and Ketones Using Me_2PPh–stabilized Cu(I) Hydride and Hydrogen..... 159

B. Investigation of Chemoselectivity and Catalytic Activity of New Catalysts..... 182

Part two. Free Radical Alkylation of Titanium(III) Allyl and Propargyl Complexes.

A. An Improved Method For The Synthesis of Titanacyclobutane Complexes 215

B. Intramolecular Free Radical Cyclizations of Titanium(III) Propargyl Complexes..... 220

C. Radical Additions of Titanium(III) Propargyl Complexes Using Cp and ^{t}BuCp Templates..... 232

IV. REFERENCES 246

List of Tables

page

Table 1. Hydrogenation catalyst for the 1,2-reduction of α,β-unsaturated aldehydes 6

Table 2. Hydrogenation catalysts for the 1,2-reduction of 3-methyl-2-butenal 8

Table 3. Catalytic hydrogenation of ketones using Me_2PPh–stabilized Cu(I) hydride and hydrogen 22

Table 4. Catalytic reduction of 4-phenyl-3-buten-2-one with $[(Ph_3P)CuH]_6$ and added phosphine 25

Table 5. *tert*–Butanol dependency test 30

Table 6. Dimethylphenylphosphine dependency test 31

Table 7. Catalytic hydrogenation of α,β-unsaturated aldehydes and ketones using Me_2PPh–stabilized Cu(I) hydride and hydrogen 40

Table 8. Synthesis data for compounds **91 - 95** 126

Table 9. Spectroscopic data for complex **96** 127

Table 10. Synthesis data for complexes **97–100** 129

Table 11. Spectroscopic data for complex **97** 130

Table 12. ^{13}C NMR Resonances of titanacyclobutene complexes **98–100** 133

Table 13. Spectroscopic data for complex **107** 142

Table 14. Spectroscopic data for complex **122** 152

List of Abbreviations

AIBN	2,2'-azobisisobutyronitrile
atm	atmosphere
bipy	2,2'-bipyridine
Bu	butyl
calcd	calculated
Cp	η^5–cyclopentadienyl
Cp*	η^5–pentamethylcyclopentadienyl
Cy	cyclohexyl
COSY	correlated spectroscopy
dba	dibenzylidene acetone
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
Et	ethyl
equiv	equivalent
g	grams
h	hour(s)
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Correlation
Hz	hertz
INAPT	Intensive Nuclei Assigned by Polarization Transfer
IR	Infrared
L	liter
M	metal
Me	methyl

mL	milliliter
MOP	Monodentate Optical Phosphine
MS	Mass spectrometry
n	normal
NMR	Nuclear Magnetic Resonance
OTf^-	Trifluoromethanesulfonate anion
Ph	phenyl
ppm	parts per million
Pr	propyl
psi	pounds per square inch gauge pressure
R	alkyl group
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tripod	1,1,1-tris(diphenylphosphinomethyl)ethane
X	halide
η	hapticity
µL	microliter

I. PART ONE

CHEMOSELECTIVE CATALYTIC HYDROGENATION OF α, β-UNSATURATED ALDEHYDES AND KETONES USING SOLUBLE COPPER(I) HYDRIDES

A. Introduction and Historical Perspective

Catalytic hydrogenation is an essential methodology for the reduction of unsaturated organic compounds. Most hydrogenation catalysts are more selective for nonpolar functionality, particularly for isolated double bonds, but less selective for polar carbon-heteroatom multiple bonds.[1,2] Thus, development of catalysts selective for the reduction of polar functionality is of considerable importance not only to synthetic chemists, but to industrial concerns as well.

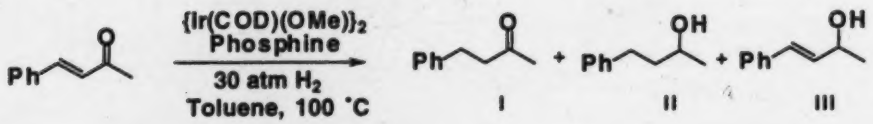
1. *Chemoselective Catalytic Reduction of α,β-Unsaturated Carbonyl Compounds*

The selectivity of transition metal catalysts has been investigated extensively. The most popular hydrogenation catalysts are heterogeneous catalysts such as Pt/C, Pd/C, and Rh/C.[3,4] These catalysts are very reactive for the hydrogenation of olefins but not reactive for the hydrogenation of carbonyl groups. Transition metal catalyzed homogeneous systems have also been reported;[1,5-10] some of them show interesting selectivity. Reger[5] reported the catalytic 1,4-reduction of α,β-unsaturated ketones to saturated ketones by using $K_3[Co(CN)_5H]$ catalyst under phase transfer conditions. Although this catalytic reaction provides a convenient method for the 1,4-reduction of α,β-unsaturated ketones, it has evident limitations, as any enone with substituents on the β-carbon can not be reduced by this catalyst system, and a double bond in conjugation with other unsaturation can be reduced at the same time.

Halpern reported the reduction of maleic acid and fumaric acid to succinic acid by a Ru(II) chloride catalyst.[6] The catalyst is selective for activated olefins; especially for electron -withdrawing group activated olefins. Olefins which are not activated by electron-withdrawing groups readily form 1 : 1 complexes with the Ru(II) species, and such olefins are difficult to reduce.

Farnetti reported the selective hydrogenation of benzylideneacetone (PhCH=CHCOMe) catalyzed by iridium phosphine systems (the catalyst was prepared *in situ* by treating $[Ir(COD)(OMe)]_2$ (COD = 1,5-cyclooctadiene) with the phosphine).[7] The investigation demonstrated that both the nature of the phosphine and the amount of added phosphine play an important role in determining the reactivity and selectivity of this catalyst system. For example, when $PMePh_2$ and the iridium complex were mixed in a ratio of 2 : 1, the reaction gave 92% saturated ketone, 5% saturated alcohol and 1% allylic alcohol after 4 h of hydrogenation (**Scheme 1, entry 1**).

Scheme 1



Entry	Phosphine	P/Ir	Conversion (h)	I	II	III
1	$PMePh_2$	2	98 (4)	92	5	1
2		3	98 (7)	26	26	46
3		5	94 (22)	11	1	82
4		10	51 (46)	0	0	51
5	PMe_2Ph	3	100 (24)	60	40	0
6		10	9 (21)	9	0	0

When $PMePh_2$ and iridium were mixed in a ratio of 3 : 1, the reaction gave 26% saturated ketone, 26% saturated alcohol and 46% allylic alcohol after 7 h of hydrogenation (**Scheme 1, entry 2**). When the ratio of $PMePh_2$ and iridium was changed to 5 : 1 , the ratio of saturated ketone : saturated alcohol : allylic alcohol was 11 : 1 : 8 after 22 h of

hydrogenation (**Scheme 1, entry 3**). When the ratio of $PMePh_2$ and iridium was changed to 10 : 1, the reaction only gave 51% allylic alcohol product after the substrate was hydrogenated for 46 h (**Scheme 1, entry 4**). Using the smaller cone angle phosphine PMe_2Ph, the reaction gave different results: when PMe_2Ph and iridium were mixed in a ratio of 3 : 1, under similar reaction conditions (30 atm pressure of hydrogen, 4 hours, 100 °C), the reaction only gave the saturated ketone and saturated alcohol in a ratio of 3 : 2; no allylic alcohol product was formed (**Scheme 1, entry 5**). When the ratio of PMe_2Ph and iridium was changed to 10 : 1, only 9% saturated ketone was obtained (**Scheme 1, entry 6**). These results demonstrated that the addition of PMe_2Ph depresses the catalytic activity, and the selective reduction of the carbonyl group in α,β-unsaturated ketones requires two conditions: one is a suitably selected phosphine ligand and the other is a high phosphine to metal ratio. Further investigation found that $[IrH_5(PR_3)_2]$ (R is alkyl or aryl) is a catalyst for hydrogenation of carbon-carbon double bonds, whereas $[IrH_3(PR_3)_3]$ is a more selective catalyst for the reduction of carbonyl group. Although some iridium-phosphine catalysts showed good selectivity for carbonyl group reduction, the results were based on a one substrate investigation and aldehyde substrates were not investigated.

In 1978, Mestroni reported the selective hydrogenation of unsaturated carbonyl compounds using rhodium(I) complexes containing the 2,2'-bipyridine(Bipy) ligand.[8] In this research, two cationic rhodium complexes, $[Rh(Bipy)S_2]^+$ and $[Rh(Bipy)_2]^+$, were investigated. The catalyst $[Rh(Bipy)S_2]^+$ (S = solvent) was made by hydrogenation of [Rh(Bipy)(1,5-hexadiene)]Cl in alkaline methanol. It was found that the *in situ* formed $[Rh(Bipy)S_2]^+$ is a good hydrogenation catalyst for the reduction of carbon-carbon multiple bond, and it showed good selectivity for the electron-withdrawing group activated carbon-carbon double bonds. For example, α,β-unsaturated esters can be reduced to corresponding saturated esters by using this catalyst. For α,β-unsaturated ketone substrates, the catalyst showed low activity; both carbonyl groups and the carbon-carbon double bonds were reduced. The catalyst $[Rh(Bipy)_2]^+$ is efficient for the reduction of

ketones, but steric effects lower the hydrogenation rate. Highly hindered ketones such as camphor do not undergo reduction. The α,β-unsaturated ketone substrate carvone was selectively reduced to dihydrocarvone when the reaction was stopped after one molar equivalent of H_2 was consumed. When the hydrogenation was allowed to proceed further, dihydrocarvol was formed exclusively.

Some anionic group VI complexes, such as $AcOM(CO)_5^-$ (M = Cr, Mo, W) have been used as homogeneous catalysts for the reduction of aldehydes and ketones.[9] Such reduction reactions require high temperature and high pressure (125 °C, 600 psi) and no selectivity studies have been reported. In 1994, Burk[10] reported a cationic rhodium(I) catalyst bearing the air-stable and crystalline diphosphine 1,1'-bis-(diisopropylphosphino)ferrocene (DiPFc). The catalyst allows the hydrogenation of aldehydes and ketones under mild conditions. Using this catalyst, most aldehydes and ketones were smoothly converted to corresponding alcohols under mild conditions (room temperature, 30 psi of hydrogen) in high yield. Because this type of catalyst had been previously used for olefin hydrogenation,[11] it is vident that the catalyst can't be used for selective reduction of enones and enals.

Highly selective catalytic 1,2-reduction of α,β-unsaturated carbonyl compounds continues to be a difficult and challenging problem since very few catalysts show good selectivity and catalytic activity for a broad range of substrates; selective reduction of α,β-unsaturated ketones is especially challenging. The selective catalytic hydrogenation of α,β-unsaturated aldehydes to unsaturated alcohols have been achieved in several instances using a variety of catalyst systems. Some of the catalyst systems can be found in early publications,[12-15] and a few important examples are listed in **Table 1.**

Table 1. Hydrogenation catalysts for the 1,2-reduction of α,β-unsaturated aldehydes

catalyst (substrate)	yield (%)	1,2- selectivity (%)	ref.
$Ru(CF_3CO_2)(CO)(PPh_3)_2$ (2-butenal)	85	60	16
$RuCl_2[PhP(CH_2CH_2PPh_2)]_2$ (2-butenal)	54	38	17
$Os(H)(Br)(CO)(PPH_3)_3$ (2-butenal)	100	50	18
$[IrCl(COD)]_2$+PPh2Cy (cinnamaldehyde)	98	96	19
$HRuCl(PPh_3)_3$ (3,7-dimethyl-2,6-octenal)	99	95	20

In 1976, Gradeff reported selective catalytic hydrogenations of α,β-unsaturated aldehydes with chromium-promoted Raney nickel in the presence of a strong inorganic base and methanol.[21] The catalyst is quite specific; substitution of the chromium-promoted Raney nickel by any other metal catalyst commonly used in catalytic hydrogenations or omission of the base or the methanol resulted in no selectivity. Alcohols other than methanol were ineffective. The catalyst system showed good selectivity for only a few substrates; for most substrates, the reaction gave low reactivity and selectivity.

In 1977, Mizoroki found that the rhodium complex $Rh_2Cl_2(CO)_4$ is effective in catalyzing selective hydrogenation of cinnamaldehyde to cinnamyl alcohol in the presence

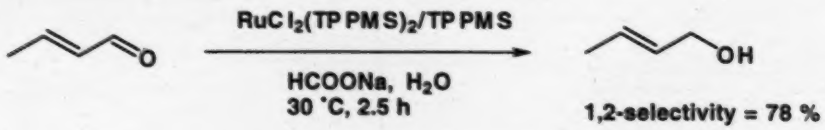
of a strongly basic amine such as triethylamine.[22] The catalyst showed good selectivity for aromatic aldehydes but low selectivity for aliphatic aldehydes. When a catalytic amount of triphenylphosphine was added to the catalyst system, the selectivity was drastically changed with only dihydrocinnamaldehyde being formed. It was concluded that the rhodium-amine-carbonyl complex is responsible for the selective hydrogenation of α,β-unsaturated aldehydes to the unsaturated alcohols.

In 1978, James found that the Henbest catalyst system[23] [$HIrCl_2(Me_2SO)_3$/propan-2-ol/aqueous acid] can convert enals into allylic alcohol products under a nitrogen atmosphere; the source of hydrogen is the alcohol solvent. With cinnamaldehyde as a substrate, the reduction goes to 90% conversion with allylic alcohol as the major product; some by-products (12%) were also produced. Since the same catalyst can also reduce the carbon-carbon double bond in α,β-unsaturated ketones,[24] it is difficult to avoid the formation of corresponding saturated alcohols when α,β-unsaturated ketones are used as substrates.[25] These results suggest that steric factors play a role in the catalytic selectivity, because the aldehyde group is less hindered compared to the ketone group. In addition, some experiment results showed that the ligand basity affects the product distribution.[22,26] Therefore, electronic factors are also important.

Metallocene complexes have also been used for the selective catalytic 1,2-reduction of α,β-unsaturated carbonyl compounds.[27] Nakano found that many enals and enones can be reduced to the allylic alcohol products by using zirconocene and hafnocene catalysts. These reactions require high temperature (130 °C) and use alcohol as the hydrogen source. For most substrates, the reaction gives good selectivity and good yield; for substrates with a terminal double bond, the reaction did not give the desired allylic alcohol product. Some reactions yielded undesired products.

Joo reported the selective reduction of enals in aqueous phase, using a water soluble ruthenium catalyst system.[28,29] The reaction can be performed under very mild

conditions (**eq. 1**) The reaction also forms sodium carbonate which makes the solution basic and deactivates the catalyst.



1,2-selectivity = 78 %

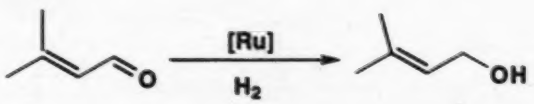
TPPMS = Tris(sulfophenyl)diphenylphosphine monosodium salt

eq. 1

Grosselin investigated other ruthenium catalysts for the 1,2-reduction of enals.[30] Selected results are listed in **Table 2**.

Table 2.

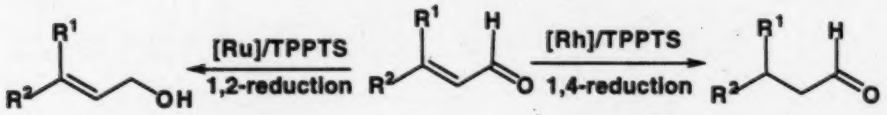
Hydrogenation catalysts for the 1,2-reduction of 3-methyl-2-butenal



catalyst	time (h)	conversion (%)	selectivity (%)
$H_2Ru(PPh_3)_4$	2	100	91
$RuCl_2(PPh_3)_3$	3	81	80
$HRuCl(CO)(PPh_3)_3$	3	33	38
$HRu(OAc)(PPh_3)_3$	7	60	73
$RuCl_3.3H_2O$	6	9	77
$RuCl_3/4PPh_3$	9	69	93

Based on the above experiments, continued research on the ruthenium catalysts was expanded to the $RuCl_3$/TPPTS (TPPTS = tris(m-sulfonylphenyl)phosphine trisodium salt) catalyst system. This catalyst showed high selectivity and good catalytic activity for the selective 1,2-reduction of enals.[30] Another interesting discovery in Grosselin's research is that it is possible to direct the hydrogenation selectivity by carefully choosing the metal. For example, enals can be reduced either into the corresponding allylic alcohol products (the 1,2-reduction) with the Ru/TPPTS system or into saturated aldehydes (1,4-reduction) with Rh/TPPTS (**Scheme 2**).

Scheme 2

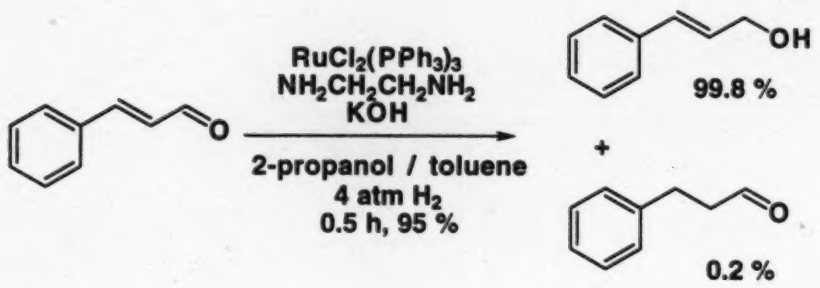


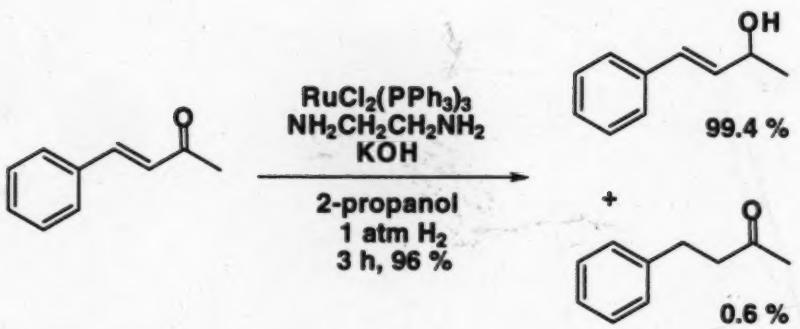
Although Grosselin's investigation showed that the $RuCl_2(PPh_3)_3$ catalyst can give 1,2-reduction of 3-methyl-2-butenal, only one substrate was tested and the generality of the catalyst is still not clear. Since some early publications revealed that the $RuCl_2(PPh_3)_3$ catalyst is a good catalyst for olefin hydrogenation,[31,32] it is difficult to imagine that such a catalyst could give a good carbonyl selectivity for all enal and enone substrates. The 1,2-selectivity in 3-methyl-2-butenal case probably arises from a steric effect, since the catalyst would prefer to access the aldehyde carbonyl group and there are two methyl groups at the β-position of the enal.

In 1995, Noyori reported a vastly improved ruthenium catalyst system, $RuCl_2(PPh_3)_3$-diamine-KOH. This catalyst system with a chiral diamine was first used in the enantioselective hydrogenation of aromatic ketones.[33] Because the catalyst showed good carbonyl selectivity in ketone reductions, it was selected for the 1,2-reduction of enals and enones. Using this catalyst system, a wide variety of conjugated and unconjugated

enal or enone substrates were selectively reduced to corresponding unsaturated alcohols (**Scheme 3**).[34]

Scheme 3



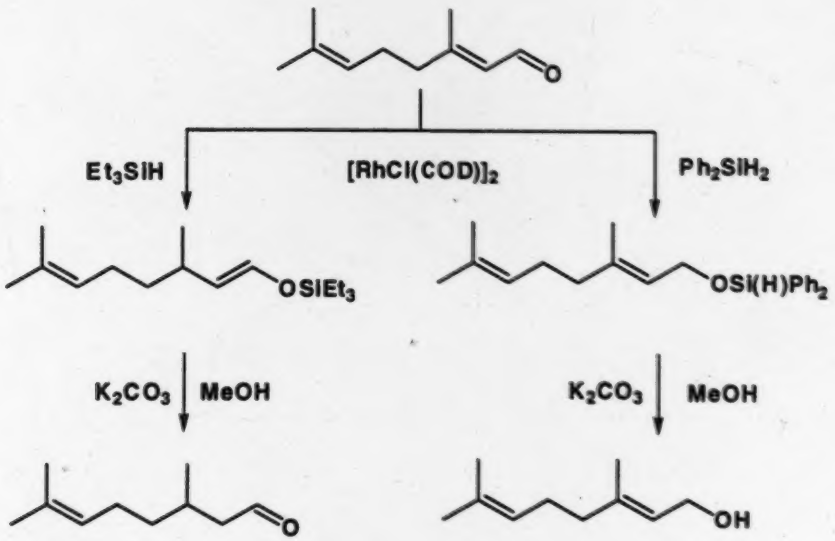


Noyori's experiments demonstrated that the combined effects of $NH_2CH_2CH_2NH_2$ and KOH decelerate olefin hydrogenation catalyzed by $RuCl_2(PPh_3)_3$ and in turn accelerate carbonyl hydrogenation; only very small amount of $NH_2CH_2CH_2NH_2$ and KOH are needed to greatly improve the selectivity. The hydrogenation reaction was performed at room temperature under 1-8 atm pressure of hydrogen. It is necessary that acidic impurities be carefully avoided.

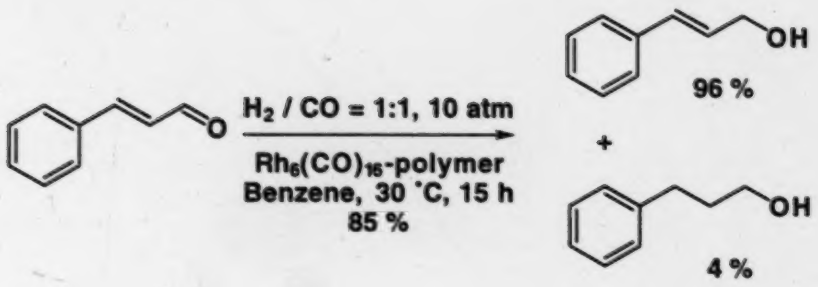
Some selective catalytic hydrosilations of unsaturated carbonyl compounds have also been reported.[35-39] In the earliest report, Ojima found that monohydrosilanes give

1,4-addition products while dihydrosilanes such as Ph_2SiH_2 give 1,2-addition products (**Scheme 4**).[39]

Scheme 4



In 1995, Zheng found that hydrosilation of α,β-unsaturated carbonyl compounds catalyzed by hydridotetrakis(triphenylphosphine)rhodium is highly regioselective.[35] The selectivity depends on the silanes used. For example, diphenylsilane give 1,2-hydrosilation, whereas dimethylphenylsilane and other monohydrosilanes give 1,4-addition. In 1996, Kaneda found that a polymer–bound rhodium carbonyl cluster catalyst can be used for selective hydrogenation of α,β-unsaturated aldehydes to allylic alcohols (**eq. 2**).[40] Using an aminated polystyrene and $Rh_6(CO)_{16}$ in the presence of H_2 and CO, various enals can be hydrogenated to allylic alcohols in high yields at 30 °C. The recovered polymer-bonded rhodium cluster catalyst can be used for another hydrogenation reaction.



eq. 2

It is evident that most hydrogenation catalysts for the selective reduction of enones and enals involve ruthenium, rhodium and iridium compounds; other metal catalysts are very rare. The search for new, versatile, and inexpensive metal catalysts capable of selective 1,2-reduction of α,β-unsaturated carbonyl compounds is still interesting and important, particularly as a new methodology for asymmetric reduction.

2. *Reduction of α,β-Unsaturated Carbonyl Compounds Using Cu(I) Hydrides*

Hexakis[hydrido(triphenylphosphine)copper(I)], $[(Ph_3P)CuH]_6$, first synthesized and structurally characterized by Osborn and Churchill in 1972,[41,42] is a useful reagent in organic synthesis.[43-52] The reagent was made originally from the reaction of $[(Ph_3P)CuCl]_4$ and $Na(CH_3O)_3BH$. This method only gave a 20% yield, and it required absolutely fresh hydride reagent. In 1981, Goeden and Caulton reported another method for the preparation of the reagent $[(Ph_3P)CuH]_6$. Triphenylphosphine complexes of copper(I) *tert*-butoxide heterolytically activate molecular hydrogen under mild conditions,

giving the thermally stable copper(I) hydride hexamer $[(Ph_3P)CuH]_6$ and *tert*-butanol (**eq. 3**).[53,54]

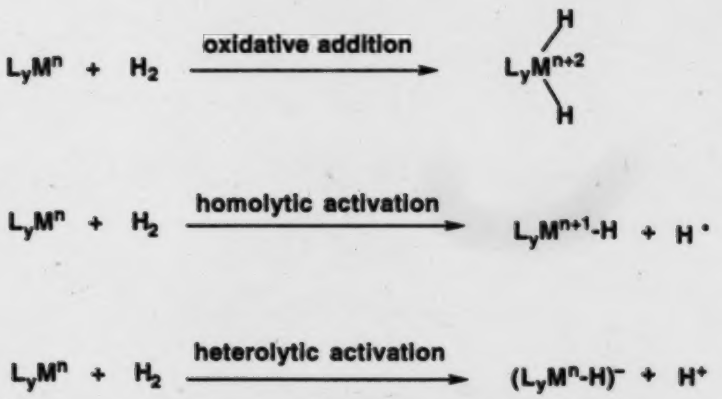
$$1/4\ (CuO^tBu)_4 + Ph_3P \xrightarrow[C_6H_6]{1\ atm\ H_2} 1/6\ [(Ph_3P)CuH]_6 + {}^tBuOH$$

eq. 3

This reaction provided the first important example of hydrogenolysis of a metal-alkoxide bond in a soluble complex. The presence of a polar copper(I)-oxygen bond, where oxygen can function as an internal base, leads to the proposal of a heterolytic mechanism for the hydrogen activation.

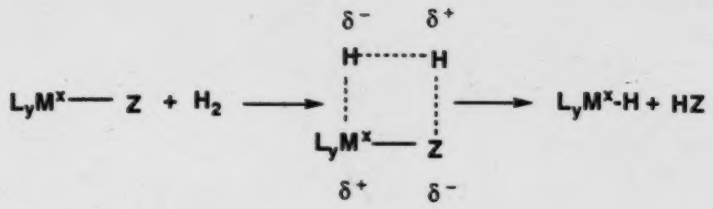
In principle, molecular hydrogen can be activated in three different ways (**Scheme 5**).[55,56] The oxidative addition pathway forms two hydride ligands on the metal and

Scheme 5



increases the oxidation state of the metal by two; electron rich low valent metal complexes favor this reaction. The homolytic activation involves hydrogen radicals and raises the oxidation state of the metal by one, it requires the metal to have two stable consecutive oxidation states. The heterolytic activation of dihydrogen leaves the oxidation state of the metal unchanged; this mechanism is most likely to be observed when the higher oxidation

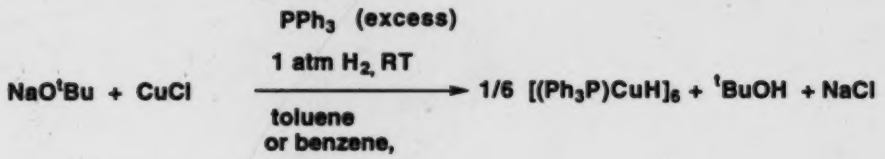
states of the metal are energetically unfavorable. For the heterolytic mechanism, the proton produced can be stabilized by the coordinated base in the reaction system (**eq. 4**).



eq. 4

Goeden and Caulton's method for the preparation of $[(Ph_3P)CuH]_6$ provides a good example of heterolytic hydrogen activation.

The most convenient method for the preparation of the reagent $[(Ph_3P)CuH]_6$ was reported by Brestensky and Stryker, by the reaction in which triphenylphosphine, copper(I) chloride and NaO^tBu are hydrogenated in toluene under one atmosphere pressure of hydrogen at room temperature (**eq. 5**).[44] The reaction can be performed on bench-top

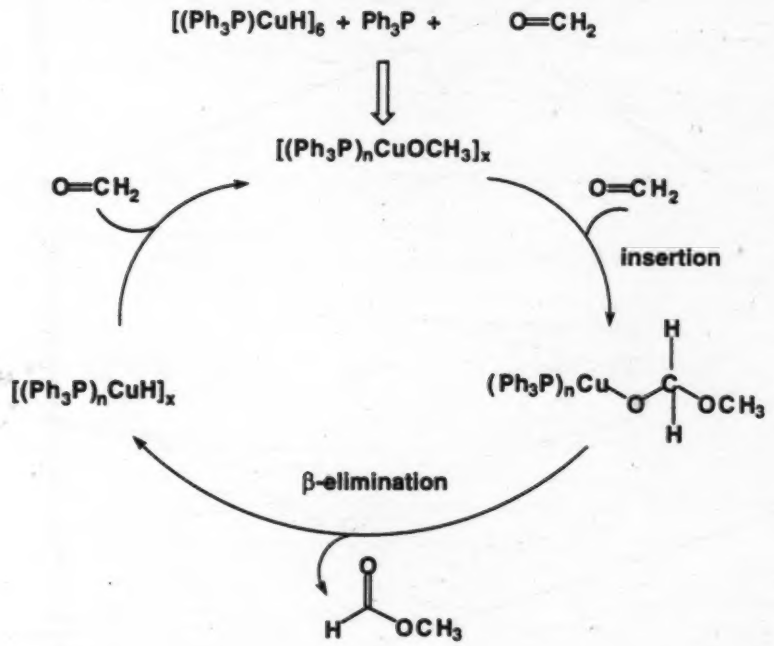


eq. 5

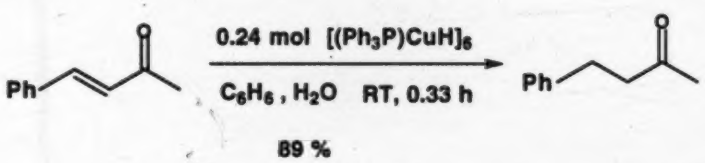
without specialized equipment, and no intermediate species need to be purified. This one-pot preparation is straightforward and inexpensive; it has been used for large-scale production and commercial scale.

Initial investigations found that $[(Ph_3P)CuH]_6$ is somewhat hydridic. For example, it can initiate the disproponation of formaldehyde to form methyl formate: the Tishchenko reaction (**Scheme 6**).[54]

Scheme 6



Early research on this complex was focused on modeling synthesis gas reactions; applications to organic reactions were never reported. In 1988, Stryker and Mahoney demonstrated that this reagent provides an effective method for selective conjugate hydride addition to α,β-unsaturated carbonyl compounds (**eq. 6**).[48]



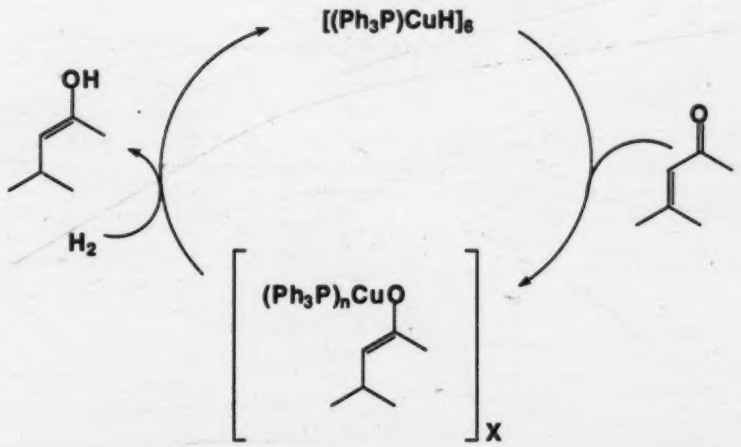
eq. 6

The reaction is performed in benzene or toluene under inert atmosphere at room temperature. All six hydrides in the reagent are delivered to the organic substrate. No 1,2-reduction product was detected, even under prolonged reaction time and in the presence of

excess $[(Ph_3P)CuH]_6$ reagent. The reagent is completely inert toward a variety of alkenes unactivated toward hydride attack; only the conjugated carbon-carbon double bond can be reduced. Isolated carbon-carbon double bonds, carbonyl groups, and a variety of typical oxygenated functionality are not reduced under the reaction conditions. In addition, the reaction is highly regioselective and stereoselective: a variety of cyclic and acyclic α,β-unsaturated carbonyl compounds were reduced in high yield, giving only the conjugate reduction product. The hydride is usually delivered to the less hindered face of the substrate.

Based on the stoichiometric reduction results and the fact that copper(I) alkoxide complexes can promote heterolytic activation of molecular hydrogen,[54,57-59] a catalytic cycle for conjugate reduction was developed (**Scheme 7**).

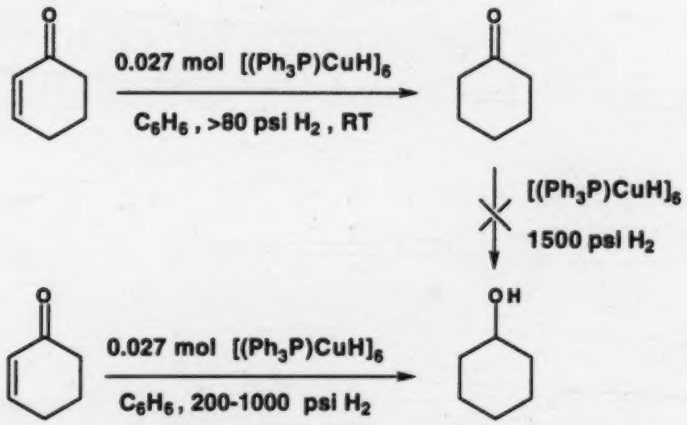
Scheme 7



In the initial test, the reaction of 2-cyclohexenone with a catalytic amount of $[(Ph_3P)CuH]_6$ under hydrogen (> 80 psi) in benzene at room temperature gave slow turnover to cycohexanone as the only product. Increasing the hydrogen pressure did improve the turnover but at the same time resulted in the formation of the saturated

alcohol product. The catalyst system, however, can not reduce cyclohexanone itself even at high pressure of hydrogen and prolonged reaction time (**Scheme 8**), although mixtures of cyclohexanone containing a small amount of cyclohexenone are completely converted to the saturated alcohol upon hydrogenation.

Scheme 8



In addition, under the reaction conditions, the catalytic reduction of enones could not be generalized. When the reaction is complete, the crude reaction mixture is heterogeneous; no $[(Ph_3P)CuH]_6$ was recovered and only some copper–containing black precipitate was recovered. The black precipitate is most probably Cu(0) from the decomposition of the postulated copper(I) enolate or alkoxide intermediates. The instability of the electron rich copper(I) oxygenates was assumed to be from the lability of the donor phosphine ligands. In order to stabilize the intermediates, excess triphenylphosphine was added to the reaction mixture. This modification proved to be very effective: the reaction mixture maintained homogeneity during the reaction process and the catalytic reduction of enones can be generalized. Using the modified method, both substituted cyclic enones and acyclic enones can be reduced catalytically to the corresponding ketones (the 1,4-reduction

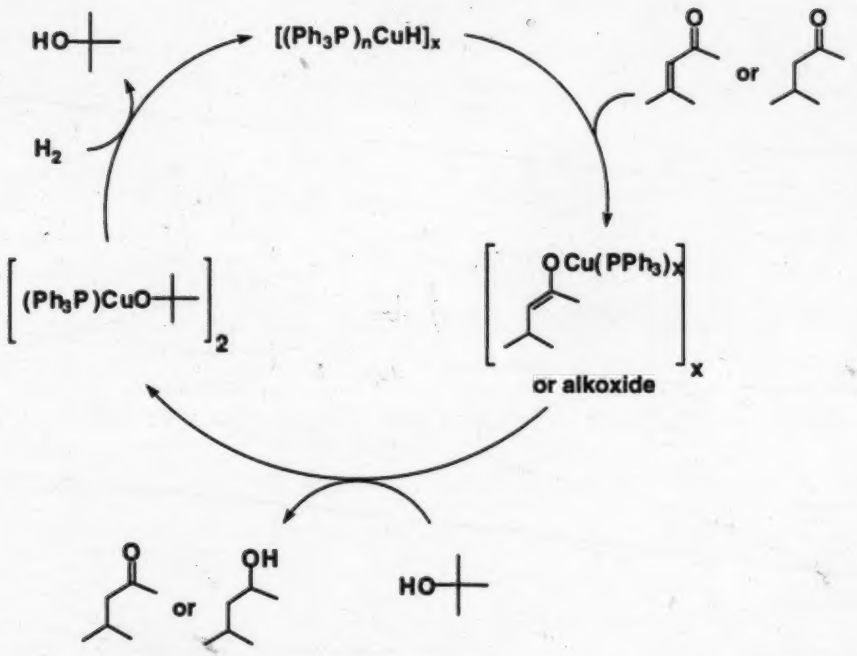
products). For cyclic enones, no direct 1,2-reduction products were observed; for acyclic enones, only a very small amount of allylic alcohol (< 10%) was formed. After complete conversion of the substrate, the $[(Ph_3P)CuH]_6$ hexamer can be recovered in high yield. The use of excess of Ph_3P, however, does inhibit the rate of conjugate reduction, presumably by inhibiting coordination of the substrate double bond.

Although the above catalytic reaction provides a practical method for enone reduction, it still has some limitations. The optimum reaction conditions are substrate dependent and, for some substrates, a large amount of excess phosphine is required to maintain the reaction system homogeneity and to inhibit catalyst decomposition. Because different substrates form different copper(I) enolate or alkoxide intermediates, the intermediates have different stabilities.

In order to quench the unstable intermediates and change the copper into a more stable form which can initiate the heterolytic hydrogen activation, *tert*-butanol was introduced into the catalytic system. The selection of *tert*-butanol was based on the fact that triphenylphosphine complexes of copper(I) *tert*-butoxide heterolytically activate molecular hydrogen under very mild conditions, giving the thermally stable copper(I) hydride hexamer $[(Ph_3P)CuH]_6$ and *tert*-butanol (**eq. 3**).[53,54] Thus, the following catalytic cycle was investigated (**Scheme 9**).

When *tert*-butanol (10-20 equiv / Cu) was added to the catalytic system, most of the enones could be reduced in high yield at atmospheric pressure of hydrogen. For example, the conjugate reduction of 3,5-dimethylcyclohexenone using 0.028 equivalents of $[(Ph_3P)CuH]_6$, triphenylphosphine (6 eq/Cu) and *tert*-butanol (10 eq/Cu), proceeded at one atmosphere of hydrogen to yield mostly cis-3,5-dimethylcyclohexanol.[51] Carvone was also reduced cleanly under these conditions. The addition of *tert*-butanol does not change the regioselectivity and stereoselectivity from that observed under *tert*-butanol free conditions. The turnover can be improved by increasing the hydrogen pressure. The mild

Scheme 9

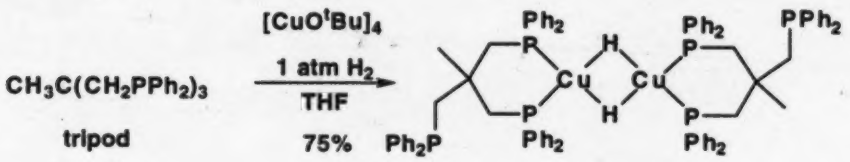


conditions, good yields, and reproducibility demonstrate that the addition of *tert*-butanol is an important improvement in the reduction procedure.

The direct catalytic hydride reduction of ketones was also investigated.[43] During the investigation of the conjugate reduction of α,β-unsaturated enones, it was found that once the coordinatively saturated hexameric aggregate has been disrupted by reduction of conjugated double bond, carbonyl reduction occurs and this second reduction is accelerated by the presence of excess triphenylphosphine. This suggests that direct carbonyl reduction is possible if the copper (I) hydride complex is hydridic enough, and if the hydridic reagent produced in solution does not form a thermodynamically very stable aggregate. There are two practical ways to produce such a hydridic reagent: (1) using a more basic ancillary

phosphine ligand and (2) using a higher concentration of phosphine to increase the number of phosphine ligands coordinated to the copper.

The dimeric copper(I) hydride complex, $[(tripod)CuH]_2$ **1** [tripod = 1,1,1-tris(diphenylphosphinomethyl)ethane], made by Caulton in 1986,[60] was first selected as a potential catalyst for direct ketone reduction. The reagent is made by hydrogenation of the complex formed between tripod and $[CuO^tBu]_4$ (**eq. 7**). In the resulting dimeric complex, two phosphine moieties are coordinated to one copper, and the two monomeric units are connected by two hydride bridges. This means that the copper would rather form bridges with the hydride ligands than coordinate the third arm of the phosphine.



1

eq. 7

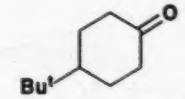
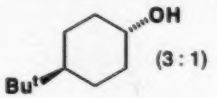
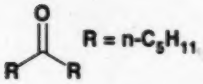
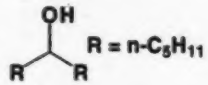
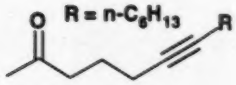
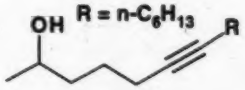
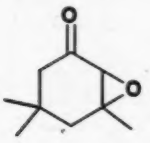
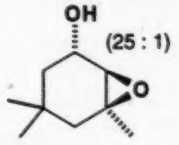
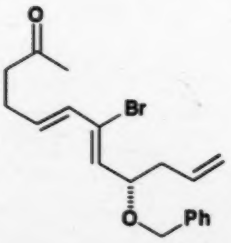
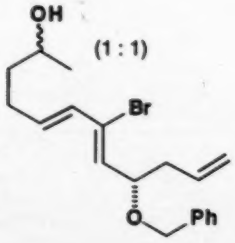
In $[(tripod)CuH]_2$, the noncoordinated third phosphine side arm provides a high local concentration of phosphine for the metal. In addition, each diphenylalkylphosphine unit is more basic than triphenylphosphine. Therefore, the $[(tripod)CuH]_2$ catalyst should be more hydridic than the $[(Ph_3P)CuH]_6$ catalyst. Using $[(tripod)CuH]_2$ as a catalyst, direct catalytic ketone reduction was observed under low hydrogen pressure. Both cyclic ketones and acyclic ketones can be reduced, with the acyclic ketone substrates reduced more slowly, requiring both longer reaction time and higher catalyst concentration. In contrast to the triphenylphosphine–coordinated catalyst, the $[(tripod)CuH]_2$ catalyst is more selective for the direct ketone reduction, but the catalyst

system needs at least two equivalents excess of the tripod ligand per copper to maintain homogeneity and sustain catalysis.

The investigation of the tripod–derived catalyst system and subsequent research indicated that coordination of more than one phosphine to the copper can make the hydride catalyst more hydridic, an important aspect for ketone reduction. In order to develop better catalytic systems for direct ketone reduction, other basic mixed alkyl-aryl monophosphine copper(I) hydride complexes were investigated. After investigation of many different phosphine coordinated copper(I) hydride catalyst systems, Daeuble found that dimethylphenylphosphine coordinated copper(I) hydride $[(Me_2PPh)_xCuH]_n$ is an excellent catalyst for chemoselective reduction of ketones under very mild conditions.[43] The active catalyst can be generated *in situ* from the ligand exchange reaction of $[(Ph_3P)CuH]_6$ and excess Me_2PPh. Complete removal of triphenylphosphine from the catalyst preparation and reduction medium can be achieved by generating the catalyst from CuCl, NaO^tBu and Me_2PPh. The catalyst system is relatively robust, but no complexes of the form $[(Me_2PPh)_xCuH]_n$ could be isolated or characterized, other than by NMR spectroscopy in solution.

A broad range of ketone substrates were reduced to corresponding alcohol products in high yield by using this catalyst system. Several selected examples are listed in (**Table 3**).[43] *tert*-Butylcyclohexanone can be reduced with less than 2 mol g% copper under atmospheric pressure of hydrogen. When the reaction is complete, addition of fresh substrate to the used catalyst system leads to complete conversion within the same time period. When the reduction reaction is performed at 50-75 psi pressure of hydrogen, it results in faster turnover. For some substrates the reduction leads to catalyst deterioration, with a copper–containing dark sediment found. However, this catalyst system demonstrates excellent chemoselectivity and stereoselectivity.

Table 3.
Catalytic hydrogenation of ketones using Me_2PPh–stabilized Cu(I) hydride and hydrogen

Entry	Substrate	Conditions[a] Time (hr)	Product(s)[b]	Yield
1		A[c], 18		97
2		B, 24		90
3		C, 12		99
4		B, 24		99
5		B, 48		83
6		C, 30		89

[a]Reaction conditions. **A**: 0.33 mol % $[(Ph_3P)CuH]_6$ (2 mol % Cu), Me_2PPh (6 equiv/Cu), one atm H_2, C_6H_6 (0.4-0.8 M in substrate), *tert*-butanol (10-20 equiv/Cu), RT. **B**: as **A**, except 0.83 mol % $[(Ph_3P)CuH]_6$ (5 mol % Cu). **C**: as **A**, except 1.67 mol % $[(Ph_3P)CuH]_6$ (10 mol % Cu). [b]Stereochemical ratio indicated in parentheses. Major stereoisomer indicated; minor product epimeric at the hydroxyl center. Relative stereochemical ratios are given in parentheses. [c]Preparation of the catalyst from CuCl and NaO^tBu (5 mol %) and Me_2PPh under hydrogen provides equivalent conversion and selectivity.

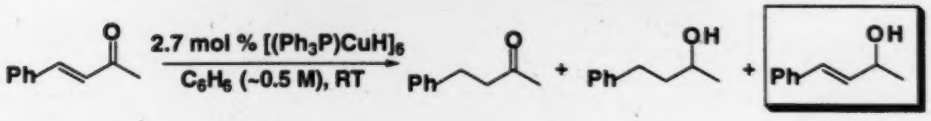
The isolated ketone can be reduced in the presence of nonconjugated alkenes, alkynes, dienes, vinylic halides, allylic oxygenates and benzylic oxygenates. These functionalities would all be reduced competitively by standard hydrogenation catalysts. Substrates with sterically unhindered alkenes require longer reaction times, probably because the isolated double bond binds competitively to the catalyst, even though it is not reduced. Interestingly, catalysts prepared from the very similar Et_2PPh ligand were completely ineffective as reduction catalysts

In summary, the $[(Ph_3P)CuH]_6$ reagent has been proven to be a very useful reagent in organic synthesis. It can be used for selective conjugate hydride addition to α,β-unsaturated carbonyl compounds, the reagent can also be used as a hydrogenation catalyst for selective 1,4-reduction of α,β-unsaturated carbonyl compounds. The $[(Me_2PPh)_xCuH]_n$ catalyst, produced *in situ* from $[(Ph_3P)CuH]_6$ and Me_2PPh, is an excellent catalyst for direct ketone reduction. It is still not clear, however, whether a copper(I) hydride reagent can be used for selective catalytic 1,2-reduction of α,β-unsaturated carbonyl compounds.

B. Project Goals

The previous work in our group has demonstrated that $[(Ph_3P)CuH]_6$ is a good catalyst for selective conjugate reduction (1,4-reduction) of α,β-unsaturated carbonyl compounds, but that it is very difficult to produce the 1,2-reduction product. In 1989, Mahoney found that the addition of excess phosphine in the catalytic reduction of 4-phenyl-3-buten-2-one gave a modest increase in the rate of turnover and also allowed for the direct 1,2-reduction of the starting enone to the corresponding allylic alcohol as a minor pathway.[49] For example, when 4-phenyl-3-buten-2-one was reduced with 2.7 mol % $[(Ph_3P)CuH]_6$ catalyst under 1000 psi of hydrogen for 10 h, all of the starting enone was converted to the saturated ketone and saturated alcohol with a ratio of the saturated ketone to saturated alcohol of 10 : 1. No allylic alcohol (1,2-reduction product) was formed (**Table 4, entry 1**). When 6 equivalents of triphenylphosphine were added to the system, under otherwise identical conditions, the reduction gave the corresponding saturated ketone, saturated alcohol, and allylic alcohol products in a ratio of 61 : 28 : 11(**Table 4, entry 2**). When the reaction time was prolonged from 10 h to 20 h, under the same conditions, no additional allylic alcohol product was produced; the reaction only gave further conversion to saturated alcohol product (**Table 4, entry 3**). When double the amount of triphenylphosphine was added to the reaction system, again no increase in allylic alcohol was observed and the reaction only gave more saturated alcohol, even at elevated hydrogen pressure (**Table 4, entries 4, 5**). When triphenylphosphine was replaced by $P(o\text{-tolyl})_3$, under otherwise the same conditions, no allylic alcohol product at all was formed (**Table 4, entry 6**). These results suggest that the triarylphosphine coordinated copper(I) hydride catalyst is not hydridic enough to perform selective 1,2-reduction of α,β-unsaturated carbonyl compounds under any conditions.

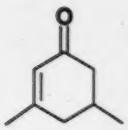
Table 4.
Catalytic reduction of 4-phenyl-3-buten-2-one with $[(Ph_3P)CuH]_6$ and added phosphine



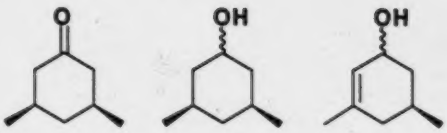
1	1000 psi H_2, 10 h,	10	1	0
2	1000 psi H_2, 10 h, 6 equiv PPh_3/Cu	61	28	11
3	1000 psi H_2, 20 h, 6 equiv PPh_3/Cu	43	49	8
4	900 psi H_2, 10 h, 12 equiv PPh_3/Cu	20	71	9
5	1700 psi H_2, 24 h, 12 equiv PPh_3/Cu	0	92	8
6	1000 psi H_2, 20 h, 6 equiv P(o-tolyl)$_3$/Cu	86	14	0

In another test, Daeuble used diphenymethylphosphine as a ligand for the catalytic reduction of 3, 5-dimethylcyclohexenone (**Scheme 10**). With 2.7 mol % $[(Ph_3P)CuH]_6$ catalyst, 6 equivalents/Cu of triphenylphosphine, 10 equivalents/Cu of *tert*-butanol, under one atmosphere of hydrogen, the saturated alcohol was obtained as the predominant product, with only a trace amount of allylic alcohol and saturated ketone detected. When triphenylphosphine was replaced by diphenylmethylphosphine, the reaction gave the allylic alcohol and the saturated alcohol in a ratio of 2.2 : 1. When the very basic trimethylphosphine was used, it resulted only in catalyst decomposition. This led us to investigate dimethylphenylphosphine, a ligand of intermediate basicity, to see whether this catalyst would give selective 1,2-reduction of α,β-unsaturated carbonyl compounds.

Scheme 10



Cat. $[(Ph_3P)CuH]_6$
1 atm H_2, C_6H_6, RT
10 equiv ^tBuOH,
6 equiv R_3P/Cu



2.7 mol % $[(Ph_3P)CuH]_6$ 6 equiv Ph_3P/Cu, 36 h	<2	:	98	:	<1
	Quantitative yield $[(Ph_3P)CuH]_6$ recovered				
1.67 mol % $[(Ph_3P)CuH]_6$ 6 equiv Ph_2PMe/Cu, 36 h	<1	:	31	:	69
			≥90%		

We have already determined that the dimethylphenylphosphine copper(I) hydride catalyst $[(Me_2PPh)_xCuH]_n$ is excellent for the chemoselective reduction of non-conjugated ketones and many common functional groups are compatible under the reaction conditions. Such good carbonyl reduction activity led us to investigate the 1,2-reduction of α,β-unsaturated carbonyl compounds using the dimethylphenylphosphine copper(I) hydride catalyst system and several related phosphine–derived catalyst systems.

The initial goal of this project was to determine whether the dimethylphenylphosphine copper(I) hydride catalyst system can be developed for the selective 1,2-reduction catalyst for α,β-unsaturated aldehydes and ketones. The second goal of this project was to investigate the relationship between ligand structure and catalyst selectivity. Both random screening and rational design techniques were used to investigate different ligand systems, to discover how steric and electronic factors affect the catalyst selectivity and activity. The third goal of this project was to provide some basic data for the development of catalytic asymmetric hydrogenation reactions. The purpose of

our ligand design is thus two-fold: one for good 1,2-selectivity, another for application to asymmetric reduction reactions. Chiral ligands were evaluated first in racemic form (considering both synthetic convenience and cost); provided the catalyst shows excellent selectivity and catalytic activity, we intended to expand our investigation into chemoselective, asymmetric hydrogenation reactions.

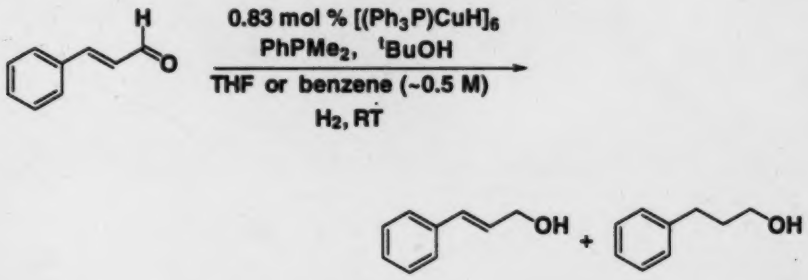
C. Results and Discussion

1. *Chemoselective Catalytic Hydrogenation of α,β-Unsaturated Aldehydes and Ketones Using Me_2PPh-Stabilized Cu(I) Hydride and Hydrogen.*

a. Investigation of the catalytic reaction conditions:

The previous investigation on the Me_2PPh–derived Cu(I) hydride catalyst was focused on the reduction of non-conjugated ketone substrates, and the results showed that the catalyst system has complete selectivity for carbonyl over nonconjugated olefin reduction. Based on this observation, this catalyst system was selected for our initial investigation of selective catalytic reduction of α,β-unsaturated aldehydes and ketones. The investigation started from the optimization of reaction conditions, which included evaluating solvent effects, *tert*-butanol dependency, phosphine concentration effects, and the effects of hydrogen pressure.

Using *trans*-cinnamaldehyde as a substrate, two different solvents, benzene and THF were tested (**eq. 8**). Thus, a solution of *trans*-cinnamaldehyde in benzene was



eq. 8

added to a catalytic amount of $[(Ph_3P)CuH]_6$ (5 mol% Cu), 6 equivalents/Cu of dimethylphenylphosphine, and 20 equivalents/Cu of *tert*-butanol in benzene solution.

The resulting solution was hydrogenated under one atmosphere pressure of hydrogen at room temperature for 3 days. Analysis of the crude mixture by ^{1}H NMR spectroscopy showed that 47% allylic alcohol product (the 1,2-reduction product) was formed, and about 50% starting material was not consumed. Only a trace amount of the saturated alcohol product was observed. The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of *trans*-cinnamaldehyde with $NaBH_4/CeCl_3$.[61] The ^{1}H NMR spectra shows characteristic doublet of triplets olefin resonances at δ 6.05 (dt, J = 15.5, 5.5 Hz, 1H) and 6.42 (dt, J = 15.5, 1.5 Hz, 1H). The allylic alcohol methylene protons appear as a doublet of doublets at δ 3.92 (dd, J = 2.8, 0.8 Hz, 2H), and the five aromatic protons appear as a multiplet at δ 6.93-7.23 (m, 5H). The saturated alcohol was identified by comparison to an authentic sample prepared by catalytic hydrogenation of the authentic allylic alcohol over Pd/C at 100 psi hydrogen pressure in ethyl acetate. The ^{1}H NMR spectra shows the presence of two benzylic protons at δ 2.50 (t, J = 7.5 Hz, 2H), and the two protons attached to the same carbon with the hydroxy group appears as a triplet at δ 3.28 (t, J = 6.5 Hz, 2H). The other two methylene protons appears as a multiplet at δ 1.62 (m, 2H), and the aromatic protons appear at δ 6.95-7.30.

The above reaction was repeated using THF as a solvent instead of benzene; under otherwise identical conditions, no improvement was observed. When the reaction time was prolonged for two more days, no further conversion was found. TLC analysis showed that most of the starting material was not consumed. As a result, for all further experiments, benzene was used as the reaction solvent.

To determine the *tert*-butanol dependency and optimize the *tert*-butanol concentration for the reaction, the reduction of *trans*-cinnamaldehyde was repeated several times with catalytic amount of $[(Ph_3P)CuH]_6$ (5 mol % Cu), 6 equivalents/Cu of dimethylphenylphosphine but different amounts of *tert*-butanol. The reaction was performed under one atmosphere pressure of hydrogen at room temperature for different

reaction times. The amount of added *tert*-butanol, the reaction time, and the allylic alcohol product yield are listed in **Table 5**.

Table 5. *tert*- Butanol dependency test.

No.	Added *tert*-butanol Equivalents/Cu	Reaction time (h)	Allylic alcohol yield (%)
1	0	72	30
2	20	72	52
3	40	3.0	60
4	60	3.0	56

When the reduction was performed in the absence of *tert*-butanol, only 30% allylic alcohol product obtained after 3 days (**Table 5, entry 1**). Some black precipitate was found after 24 h, indicating catalyst deterioration. When 20 equivalents/Cu *tert*-butanol was added, the reaction gave 52% allylic alcohol product after 3 days (**Table 5, entry 2**) and only a trace amount of saturated alcohol product was observed. The remaining material consisted only of the starting material. When 40 equivalents/Cu *tert*-butanol was added, 60% allylic alcohol was obtained in only 3 h (**Table 5, entry 3**). After that time the reaction continued to proceed very slowly, indicating the catalyst deactivation. Increasing the *tert*-butanol concentration to 60 equivalents/Cu, the reaction gave similar results to the 40 equivalents/Cu *tert*-butanol case, indicating that 40 equivalents/Cu *tert*-butanol is the saturation limit for the catalyst system. Based on these experimental results, the amount of added *tert*-butanol was set at 40 equivalents/Cu.

In the dimethylphenylphosphine dependency test, we had already determined that without added dimethylphenylphosphine, the catalytic reduction of α,β-unsaturated aldehydes and ketones using $[(Ph_3P)CuH]_6$ only gives the 1,4-reduction product (*vide*

supra). When less than 3 equivalents/Cu dimethylphenylphosphine was added to the catalyst system, catalyst deterioration occurs after several hours of reduction, and the reaction gave low selectivity and low turnover.[43] Thus, our investigation started from using 4 equivalents/Cu of added dimethylphenylphosphine. The reduction of *trans*-cinnamaldehyde was repeated several times with catalytic amount of $[(Ph_3P)CuH]_6$ (5 mol% Cu), 4 - 12 equivalents/Cu of dimethylphenylphosphine, and 40 equivalents/Cu of *tert*-butanol. The reaction was performed under one atmosphere pressure of hydrogen at room temperature for different time periods and the results are listed in **Table 6**

Table 6. Dimethylphenylphosphine dependency test

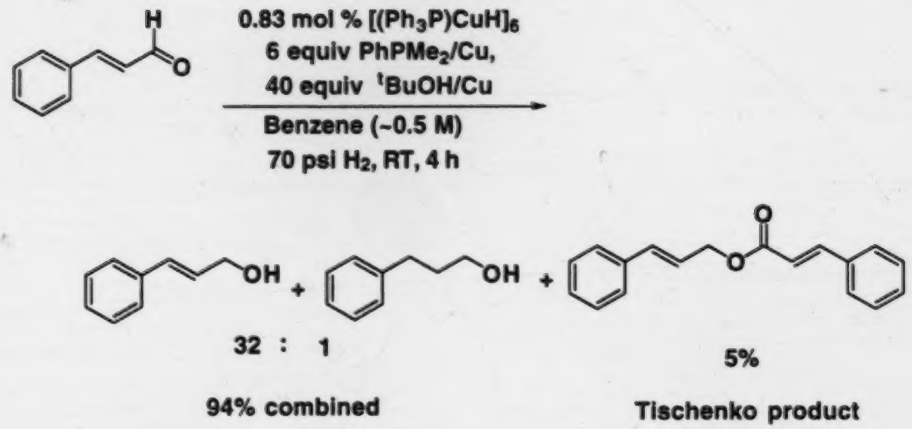
No.	Added $PhP(Me)_2$ Equivalents/Cu	Reaction time (h)	Allylic alcohol yield (%)
1	4	24	60
2	6	3.0	60
3	12	20	21

When 4 equivalents/Cu dimethylphenylphosphine was added, the reaction solution initially turned to brown. After six hours, it became a little darker, and at the end of the reaction (24 h), the system had turned a little heterogeneous. After 24 h, 60% allylic alcohol was recovered (**Table 6, entry 1**); the remaining material was the starting cinnamaldehyde. Under the same reaction conditions, using 6 equivalents/Cu dimethylphenylphosphine, the reaction solution maintained the yellow-brown color and stayed homogeneous throughout the reaction process. After three hours 60% allylic alcohol product was obtained (**Table 6, entry 2**). The improved turnover lead us to continue to increase the amount of added dimethylphenylphosphine to 12 equivalents/Cu. However, when the substrate was combined with the catalyst system, the solution color

turned dark brown and several hours later, a black tarry substance was formed in the reaction solution. After standard work-up, only 21% of the allylic alcohol was obtained (**Table 6, entry 3**). Based on these experimental results, the amount of added dimethylphenylphosphine was set at 6 equivalents/Cu.

In the above tests, most of the catalytic reactions did not go to completion, even under prolonged reaction time and optimized *tert*-butanol and dimethylphenylphosphine concentrations. We thought that higher pressure of hydrogen may be the most practical solution to this problem. Since the reaction between hydrogen and the intermediate copper alkoxide complex is a bimolecular reaction, increased hydrogen pressure will result in an increase in the hydrogen concentration in the fixed reaction vessel. The increased hydrogen concentration will favor productive heterolytic hydrogen activation over decomposition of the intermediate and facilitate the regeneration of the copper(I) hydride catalyst. Goeden and Caulton have shown that the rate for the hydrogenolysis of the copper-oxygen bond in triphenylphosphine stabilized $(CuO^tBu)_4$ is proportional to the pressure of hydrogen.[62] Thus, the reduction reaction was performed under elevated hydrogen pressure. Using a catalytic amount of $[(Ph_3P)CuH]_6$, 6 equivalents/Cu of dimethylphenylphosphine and 40 equivalents/Cu of *tert*-butanol, *trans*-cinnamaldehyde was hydrogenated in benzene under 70 psi pressure of hydrogen for 4 h. TLC analysis showed complete conversion and the ^1H NMR spectrum of the crude product mixture showed the presence of allylic alcohol and the saturated alcohol in a ratio of 32 : 1. This ratio demonstrates that the catalyst system is highly selective for the 1,2-reduction of the enal substrate. The crude reaction mixture was purified via short–path silica gel flash chromatography to afford the inseparable allylic alcohol and saturated alcohol products in a 94% isolated yield (**Scheme 11**). The allylic alcohol product and the saturated alcohol product were identified by comparison to authentic samples (*vide supra*). Another minor product (isolated in 5% yield) was tentatively identified as the Tischenko reaction product $PhCH{=}CHCH_2OC(O)CH{=}CHPh$, based on analysis of the ^1H NMR spectrum.

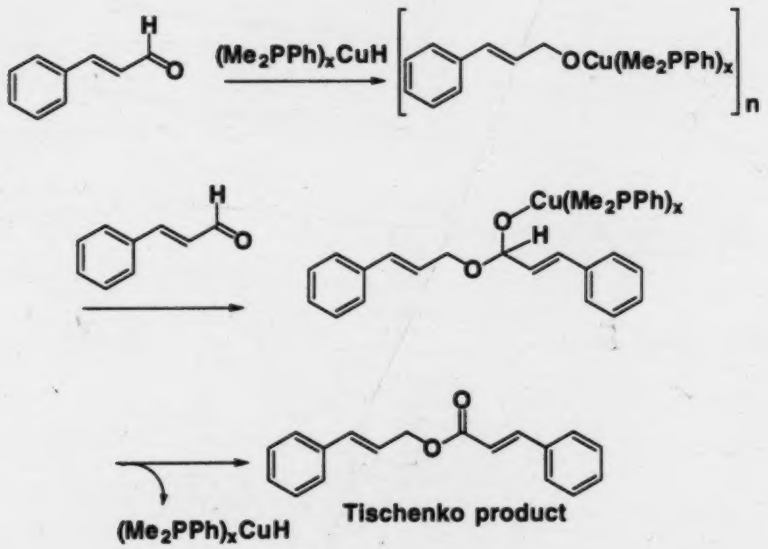
Scheme 11



The characteristic resonances for the two methylene protons appears as a dd at δ 4.75 (dd, J = 7.5, 1.5 Hz, 2H); one olefin proton appears as a dt at δ 6.20 (dt, J = 15.5, 7.5 Hz, 1H), and the other three olefin protons appear as a doublet at δ 6.49 (d, J = 15.5 Hz, 1H), 6.68 (d, J = 15.5 Hz, 1H) and 7.85 (d, J = 15.5 Hz, 1H). The coupling constants between the olefin protons are around 15 Hz, indicating the two olefins are trans–olefins. In addition, the aromatic protons appear at δ 6.9-7.3. The Tischenko product is most probably formed via the following route (**Scheme 12**).

The Tischenko product was also observed in the catalytic reduction of aldehydes using the [1,1,1–tris(diphenylphosphinomethyl)ethyl] coordinated copper(I) hydride, $[(tripod)CuH]_2$. Brestensky found that when benzaldehyde was reduced, the reaction gave two products: benzyl alcohol and the Tischenko product benzyl benzoate. A similar mechanism was proposed (**Scheme 13, entries 1, 2**).

Scheme 12



Early investigation of copper(I) hydride chemistry also found Tishchenko products from aldehyde reduction. Goedon and Caulton found that the reaction of $[(Ph_3P)CuH]_6$ with formaldehyde produces methyl formate (**Scheme 6**).[54] The original Tishchenko reaction involved the reaction of aldehyde and an aluminum alkoxide: when aldehydes were treated with aluminum ethoxide, one aldehyde molecule was oxidized and another was reduced to afford the corresponding ester (**eq. 9**)[63].

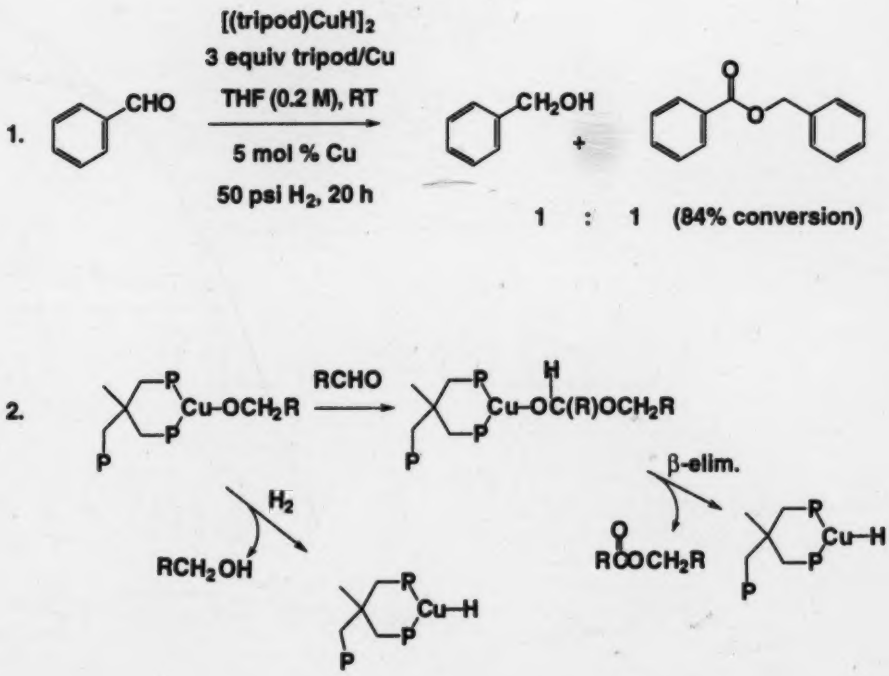
$$2RCHO \xrightarrow{Al(OEt)_3} RCOOCH_2R$$

eq. 9

Although the catalytic reduction of *trans*-cinnamaldehyde using the dimethylphenylphosphine derived copper(I) hydride catalyst system gave 3 products (**Scheme 11**), the 1,2-reduction product is predominant (> 90% isolated). In complete

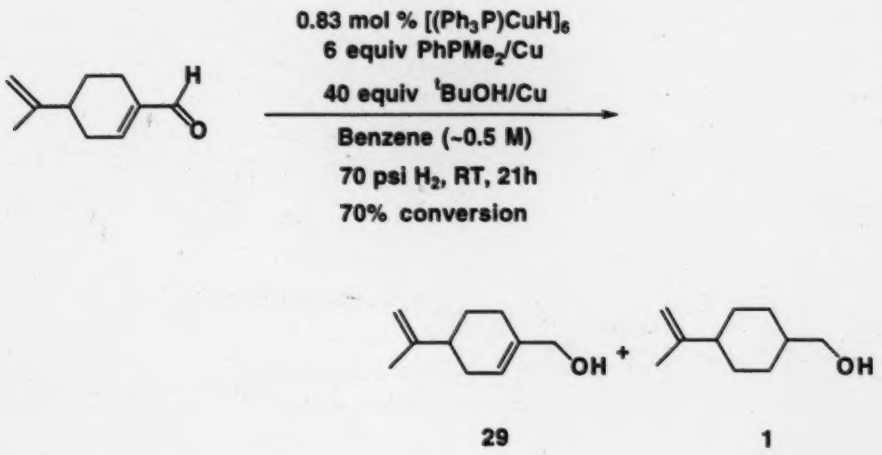
contrast to the one atmosphere pressure reaction, which does not go to completion even at prolonged time, the 70 psi hydrogen reaction proceeds smoothly and goes to completion at greatly accelerated rate (4 h). Most importantly, the reaction also showed high selectivity for the carbonyl group of the α,β-unsaturated aldehyde substrate. Thus, this experiment confirmed that elevated hydrogen pressure can accelerate the hydrogenation reaction and give higher turnover.

Scheme 13



To investigate the generality of the low pressure hydride mediated catalytic reduction of α,β-unsaturated aldehydes using the dimethylphenylphosphine–stabilized copper(I) hydride, another substrate, perillaldehyde, was tested. This α,β-unsaturated aldehyde substrate has an isolated carbon-carbon double bond, thus it is of interest to determine whether the isolated double bond is reduced under these reaction conditions.

Using the same reaction conditions, perillaldehyde was hydrogenated under 70 psi pressure of hydrogen for 21h (**eq. 10**). The crude ^{1}H NMR spectrum showed the

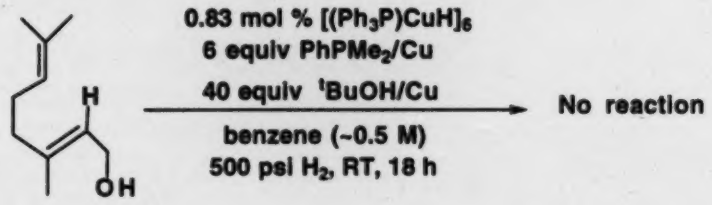


eq. 10

presence of the combined alcohols (the allylic alcohol and the saturated alcohol) and the starting material in a ratio of 70 : 30; the allylic alcohol and the saturated alcohol were formed in an excellent ratio of 29 : 1. Although the reaction resulted in good 1,2-selectivity, it did not go to completion, even after 21 h. In a modified experiment, the reaction solution was hydrogenated under 500 psi pressure of hydrogen in a stainless steel autoclave. After 18 h, analysis of the crude ^{1}H NMR spectrum showed the presence of allylic alcohol and the saturated alcohol in a ratio of 32 : 1, with all of the starting material consumed. The products were isolated via chromatography giving the inseparable allylic alcohol and saturated alcohol products in 95% isolated yield. The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of perillaldehyde with $NaBH_4/CeCl_3$.[61] The saturated alcohol product was identified by comparison to an authentic sample.[64] In contrast to the reduction of *trans*-cinnamaldehyde, the reduction of perillaldehyde requires a higher pressure of hydrogen.

This is probably due to the competitive coordination between the isolated carbon-carbon double bond and the copper(I) metal, as such coordination inhibits the rate of the catalytic reduction.

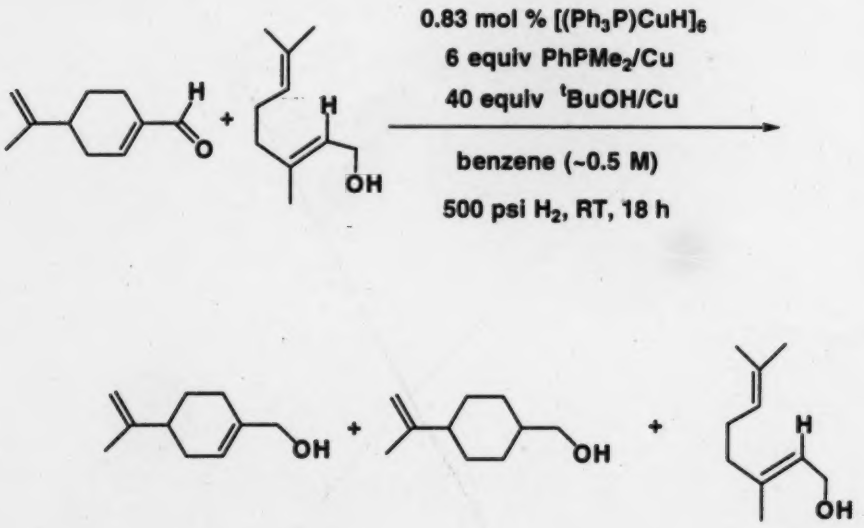
As catalytic reductions of α,β-unsaturated aldehydes give the corresponding allylic alcohols as the major products and the saturated alcohols as the minor products, it is important to determine whether the allylic alcohol can be reduced to the corresponding saturated alcohol under the reaction conditions. To investigate this possibility, the reduction of geraniol was undertaken (**eq. 11**). The reaction was purposefully performed under high pressure and prolonged reaction time, to see if further reduction products could be produced. Thus, geraniol was combined with a benzene solution of $[(Ph_3P)CuH]_6$, 6 equivalents/Cu of dimethylphenylphosphine and 40 equivalents/Cu. of *tert*-butanol. The resulting mixture was hydrogenated under 500 psi of hydrogen for 18 h. However, analysis of the crude mixture by ^1H NMR spectroscopy indicated that no reduction occurred, and all starting material was recovered (**eq. 11**).



eq. 11

To further examine the selectivity and also to provide insight into the formation of the saturated alcohol under the reaction conditions, the catalytic reduction of perillaldehyde was performed in the presence of geraniol. This experiment was designed to examine if some *in situ* produced reactive intermediates can facilitate the reduction of the allylic alcohol to the corresponding saturated alcohol. As seen in equation **12**, when a solution of perillaldehyde and geraniol was hydrogenated under 500 psi of hydrogen for

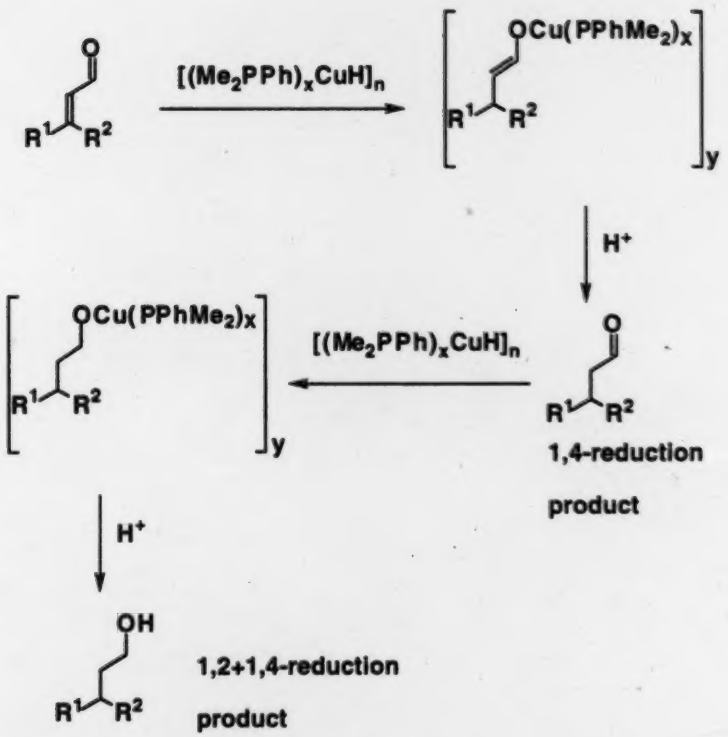
18 h, no hydrogenation of geraniol was observed and all of the perillaldehyde was reduced to the corresponding allylic alcohol along with only a trace amount of the saturated alcohol produced, as indicated by the crude ^{1}H NMR spectrum. The ratio of the two alcohol products was similar to the ratio obtained in the reduction performed in the absence of geraniol (> 30 : 1). No hydrogenation of geraniol was observed.



eq. 12

These results indicate that the saturated alcohol product (1,2+1,4-reduction product) is not formed from the continued reduction of the first–formed allylic alcohol product. Under these reaction conditions, the $[(Me_2PPh)_xCuH]_n$ catalyst system can't reduce allylic alcohols to the corresponding saturated alcohols. Therefore, the saturated alcohol product most probably arises from the further reduction of the minor first–formed saturated aldehyde (the 1,4-reduction product), as depicted in **Scheme 14**. Because we have determined that this catalyst system is highly reactive toward the direct carbonyl reduction of unconjugated ketones, the direct reduction of any saturated aldehyde is also expected.

Scheme 14



Zavalii and coworkers demonstrated that an allylic alcohol can coordinate to simple copper (I) complexes.[65] Hence, it is reasonable to assume that the allylic alcohol product coordinates with some copper (I) species, but such coordination does not result in further reaction.

b. 1,2-Reduction of α,β-unsaturated aldehydes and ketones

After the catalytic reaction conditions were optimized, additional substrates were evaluated, including various α,β-unsaturated ketones. The results are compiled in **Table 7.**

Table 7.

Catalytic hydrogenation of α,β-unsaturated aldehydes and ketones using Me_2PPh–stabilized Cu(I) hydride and hydrogen

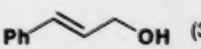
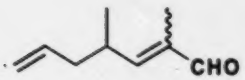
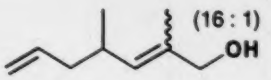
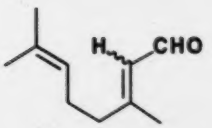
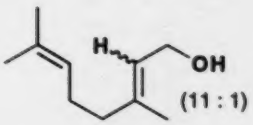
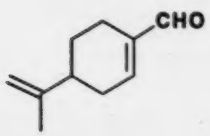
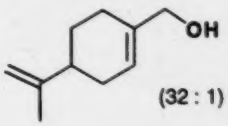
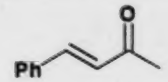
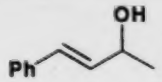
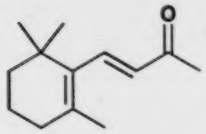
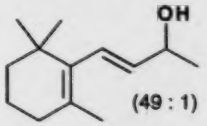
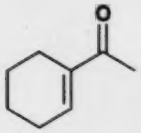
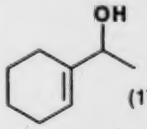
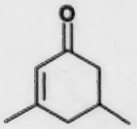
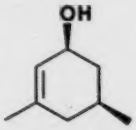
Entry	Substrate	Conditions[a] Time (hr)	Product(s)[b,c]	Yield[d]
1		A, 4	 (32 : 1)	94[e]
2[f]		B, 30	 (16 : 1)	91[f]
3[g]		C, 15	 (11 : 1)	90[g]
4		C, 18	 (32 : 1)	95

Table 7 continued

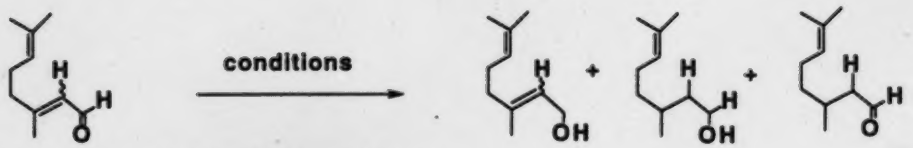
5		C, 18	 (12 : 1)	81[h]
6		C, 26	 (49 : 1)	89
7		C, 20	 (17 : 1)	94
8		C, 30	 (2.7 : 1)[i]	90
9		D, 24	(4.4 : 1)[i]	92

[a]Reaction conditions. **A**: 0.83 mol % $[(Ph_3P)CuH]_6$ (5 mol % Cu), Me_2PPh (6 equiv/Cu), 70 psi H_2, C_6H_6 (0.4-0.8 M in substrate), *tert*-butanol (40 equiv/Cu), RT. **B**: as **A**, 400 psi H_2. **C**: as **A**, except 500 psi H_2. **D**: as **A**, except copper introduced as CuCl (5 mol%) with NaO^{t}Bu (5 mol%), 1000 psi H_2. [b]Major product indicated; minor product is saturated alcohol (1,4 + 1,2 reduction). Product ratio is given in parentheses. [c]Products identified by comparison with authentic materials prepared by unambiguous synthesis (see experimental section). [d]Isolated yields after purification by chromatography. [e]Remaining material tentatively identified (NMR spectroscopy) as the Tischenko reaction product $PhCH{=}CHCH_2OC(O)CH{=}CHPh$. [f]E/Z = 10 : 1 (substrate), 10 : 1 (product). [g]E/Z = 2 : 1 (substrate and product). [h]Isolated yield after acetylation (Ac_2O/pyridine) and purification. [i]Major stereoisomer indicated (12 : 1); minor epimeric at hydroxyl center.

In all cases, the reactions gave high yields of alcohol products. Typically, two alcohol products, the allylic alcohol (1,2-reduction product) and the saturated alcohol (1,2+1,4-reduction product) were obtained as an inseparable mixture and were purified from by–products by flash column separation. All of the reduction reactions using α,β-unsaturated aldehydes gave excellent 1,2-selectivity under the indicated reaction

conditions and the ratios of allylic alcohol to corresponding saturated alcohol were always greater than 10 : 1 (**entries 1-4**). Isolated double bonds were not reduced (**entries 2-4**). Taking the reduction of citral as an example (**entry 3, and Scheme 15, entry1**), when the combined solution of substrate and catalyst was hydrogenated under 500 psi pressure of hydrogen for 15 h, two alcohol products were obtained in 90% isolated yield. The major product (> 90%) is the allylic alcohol, and the minor product (< 10%) is the corresponding saturated alcohol. In complete contrast, the same reduction reaction performed by using $[(Ph_3P)CuH]_6$ and excess triphenylphosphine instead of dimethylphenylphosphine produced only a trace amount of the allylic alcohol product; most of the starting material was not consumed (**Scheme 15, entry 2**).

Scheme 15



(1) 0.83 mol % $[(Ph_3P)CuH]_6$, 6 equiv $PhPMe_2$/Cu, 40 equiv ^tBuOH/Cu, Benzene (~0.5 M), 500 psi H_2, RT, 15 h — 11 : 1 : 0, 90% combined yield

(2) 0.83 mol % $[(Ph_3P)CuH]_6$, 6 equiv $PhPMe_2$/Cu, 40 equiv ^tBuOH/Cu, benzene, 500 psi H_2, RT, 25 h — trace (remainder starting material)

(3) 0.2 mol $[(Ph_3P)CuH]_6$, 20 equiv H_2O, Benzene, RT, 1.5 h — trace : minor : major

(4) 0.4 mol $[(Ph_3P)CuH]_6$, 20 equiv H_2O, Benzene, RT, 32 h — trace : major (74%) : 0

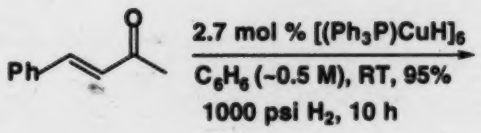
Brestensky and Stryker found that when citral was reduced with a stoichiometric amount of $[(Ph_3P)CuH]_6$ in the presence of a small amount of water, saturated aldehyde was obtained as the major product; along with a small amount of the saturated alcohol and a trace amount of allylic alcohol. Using a large excess of $[(Ph_3P)CuH]_6$, the complete reduction occurred and only the saturated alcohol was obtained (**Scheme 15, entries 3, 4**).[45] When chlorotrialkylsilane was added to the above reaction mixture, no allylic alcohol could be detected and the substrate was reduced to the silyl enol ether in quantitative yield.

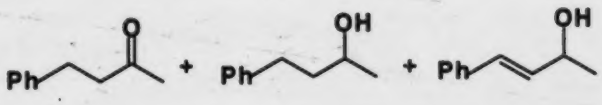
The citral reduction experiments demonstrate that when triphenylphosphine is replaced by dimethylphenylphosphine, an obviously different catalyst system is formed. The dimethylphenylphosphine derived copper(I) hydride system is more hydridic and more selective for 1,2-reduction of α,β-unsaturated carbonyl compounds, giving allylic alcohol as the major reduction product. In contrast, the triphenylphosphine stabilized copper(I) hydride catalyst system is not reactive enough to reduce the α,β-unsaturated aldehydes, despite the earlier experimental results demonstrate that the $[(Ph_3P)CuH]_6$ reagent is a versatile stoichiometric reagent for the reduction of α,β-unsaturated aldehydes. Under stoichiometric conditions, depending on the amount of added $[(Ph_3P)CuH]_6$, the reduction gives either the 1,4-reduction product (the saturated aldehyde) or the 1,2+1,4-reduction product (the saturated alcohol), but no 1,2-reduction product (the allylic alcohol).

The reduction of α,β-unsaturated ketones using the dimethylphenylphosphine stabilized copper(I) hydride catalyst system was also investigated. The results showed that the catalytic reduction of acyclic conjugated enones gives very good 1,2-selectivity, with the allylic alcohols obtained as the predominant products (> 90%). The only other products obtained are the corresponding saturated alcohols (<10 %). For example, the

catalytic reduction of β-ionone under standard conditions gave the allylic alcohol and the saturated alcohol in a ratio of 49 : 1 (**Table 7, entry 6**). The reduction of 1-acetyl-1-cyclohexene and *trans*-4-phenyl-3-buten-2-one also gave good 1,2-selectivity under the same reaction conditions (**Table 7, entries 5, 7**). In contrast, when the *trans*-4-phenyl-3-buten-2-one was reduced with a catalytic amount of $[(Ph_3P)CuH]_6$ (without any added phosphine) under 1000 psi pressure of hydrogen, the major product was the 1,4-reduction product; no 1,2-reduction product was formed (**Scheme 16, entry 1**). When the same reaction was performed with 12 equivalents/Cu added triphenylphosphine, the reaction gave the 1,2+1,4-reduction product as the major product (**Scheme 16, entry 2**).[50] These experiment results demonstrate the flexibility of Cu(I)–catalyzed hydrogenation obtained by changing the reaction conditions.

Scheme 16





1.	No PPh_3	10	1	0
2.	12 equiv PPh_3/Cu	2	7	1
3.	6 equiv Me_2Ph/Cu	0	1	12

The reduction of cyclic ketones is more variable. The lowest selectivity was obtained in the reduction of cyclohexenone derivatives, which also showed a significant residual influence of the triphenylphosphine present in catalysts prepared by ligand

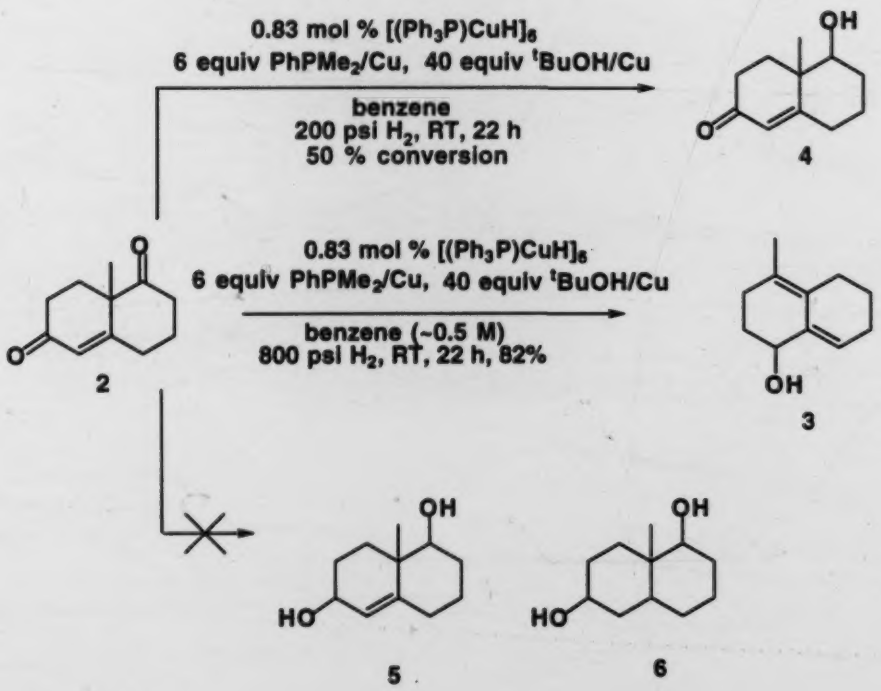
exchange. For example, 3,5-dimethylcyclohexenone was combined with a benzene solution of catalytic amount of $[(Ph_3P)CuH]_6$, 6 equivalents/Cu of dimethylphenylphosphine, and 40 equivalents/Cu of *tert*-butanol and the resulting mixture was hydrogenated under 500 psi pressure of hydrogen for 30 h. A mixture of two products, the allylic alcohol and the saturated alcohol was obtained in 90 % combined yield (**Table 7, entry 8**). Analysis of the crude mixture by ^1H NMR spectroscopy showed the presence of allylic alcohol and saturated alcohol in a ratio of only 2.7 : 1. In another experiment, the catalyst was prepared from CuCl and NaO^tBu in the presence of dimethylphenylphosphine. The catalyst prepared in this way completely removes triphenylphosphine from reaction mixture. Using this catalyst system, 3,5-dimethylcyclohexenone was hydrogenated under 500 psi pressure of hydrogen for 24 h. The corresponding allylic alcohol product and saturated alcohol product were obtained in 92 % combined yield, and the crude ^1H NMR spectrum showed the presence of allylic alcohol and saturated alcohol in an improved ratio of 4.4 : 1 (**Table 7, entry 9**). Hence, the catalyst system derived from CuCl and NaO^tBu is more selective and more reactive than the catalyst derived from $[(Ph_3P)CuH]_6$ and dimethylphenylphosphine.

In order to further investigate this hydride mediated catalytic reaction process and develop it into practical methodology for organic synthesis, catalytic reductions of more complicated α,β-unsaturated ketone substrates were undertaken. Wieland-Miescher ketone **2** has two different carbonyl groups, one isolated and the other conjugated with the carbon-carbon double bond. It is of interest to know which carbonyl group will be reduced preferentially under standard reaction conditions. Thus, the Wieland-Miescher ketone **2** was combined with the catalyst system derived from $[(Ph_3P)CuH]_6$ and added dimethylphenylphosphine and the resulting solution was hydrogenated under 500 psi pressure of hydrogen for 24 h. The crude ^1H NMR spectrum and TLC analysis showed that the reaction mixture contains more than four different products which were difficult to isolate and identify. Using THF as a solvent instead of benzene, the reaction still gave

a complicated mixture. When the reaction was performed under lower hydrogen pressure (200 psi), the crude ^1H NMR spectrum showed about 50 % conversion, alcohol **4** was the only product (**Scheme 17**). Reduction of Wieland-Miescher ketone **2** with $NaBH_4$ also gives compound **4** selectively.[66]

When the catalytic reaction was performed under 800 psi pressure of hydrogen for 22 h at room temperature, a product of an unusual rearrangement was formed in 82 % yield (**Scheme 17**). The formation of compound **3** was clearly not anticipated. Initially, we proposed that the major products of this reaction would be the simple ketone reduction products **5** and **6**, but these two products were not detected in the reaction mixture.

Scheme 17

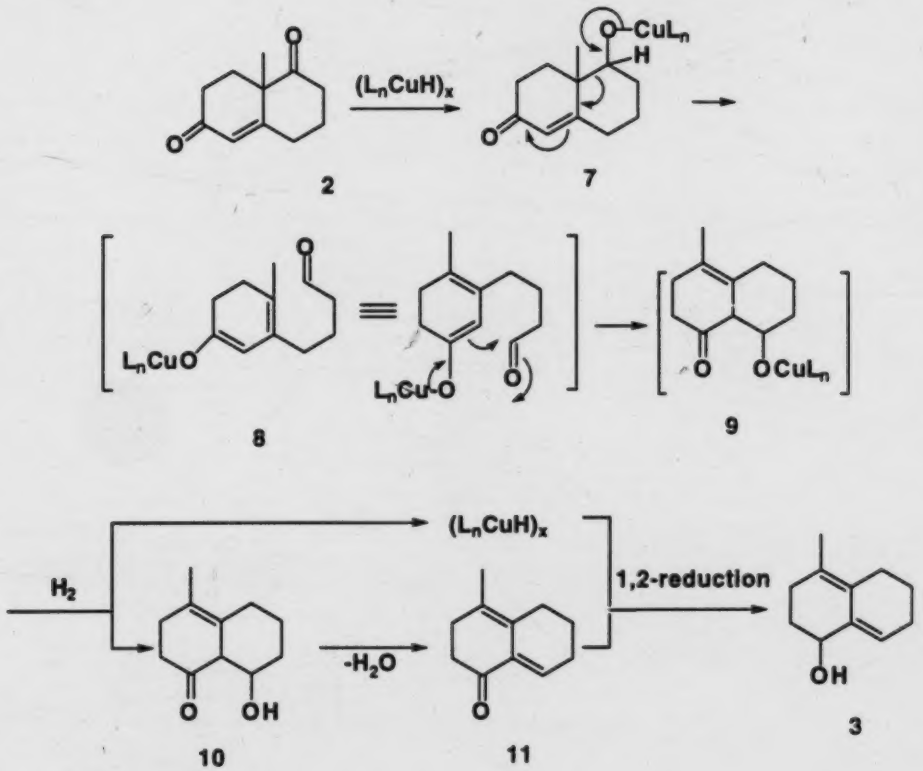


The structure assignment of compound **3** is based on an analysis of the spectroscopic data. The ^1H NMR spectrum indicated the signal for the olefin proton at δ

5.71 (t, J = 4.0 Hz, 1H), the triplet multiplicity is inconsistant with the expected products **4** and **5**. This assignment was confirmed by two dimensional HMQC, INAPT and HMBC spectra. In the HMQC spectrum, this proton is correlated to the carbon at δ 122.8. In an INAPT experiment, when this proton was irradiated, four carbon signals appeared at δ 125.4, 70.1, 25.5, 22.8. This result fits the structure **3**. The HMBC spectrum confirmed this connectivity. The signals for the methine proton attached to the carbon bearing the hydroxy group appears at δ 4.19 (t, J = 3.6 Hz, 1 H). In the HMQC spectrum, this proton is correlated to the carbon at δ 70.2. In the INAPT experiment, when this proton was irradiated, five carbon signals appear at δ 137.4, 125.4, 122.8, 30.4, 28.6. The HMBC spectrum confirmed this connectivity, althrough the correlation to the δ 30.4 signal was not observed. The IR spectrum indicated the presence of the hydroxy group; no carbonyl group peak was observed. The remaining signals and spectroscopic data are fully consistent with the assigned structure.

To explain the formation of this unusual product, the following mechanism is proposed (**Scheme 18**). The isolated carbonyl group of the Wieland-Miescher ketone **2** is reduced first by the copper (I) hydride reagent, forming the copper alkoxide intermediate **7**, consistant with the product obtained at lower pressure. Retro-adol fragmentation of the copper alkoxide results in ring opening and rearrangement to afford the copper (I) dienolate **8**. Intramolecular ring closure of the copper (I) enolate **8** gives the rearranged copper alkoxide complex **9**. Heterolytic hydrogen activation by complex **9** results in the formation of the β–ketoalcohol **10** and at the same time regenerates the copper (I) hydride catalyst. Dehydration of compound **10**, presumably catalyzed by a Cu(I) alkoxide base, gives ketone **11**. Finally, ketone **11** and the copper(I) hydride catalyst undergo a highly selective 1,2-reduction to afford the final product **3** (**Scheme 18**).

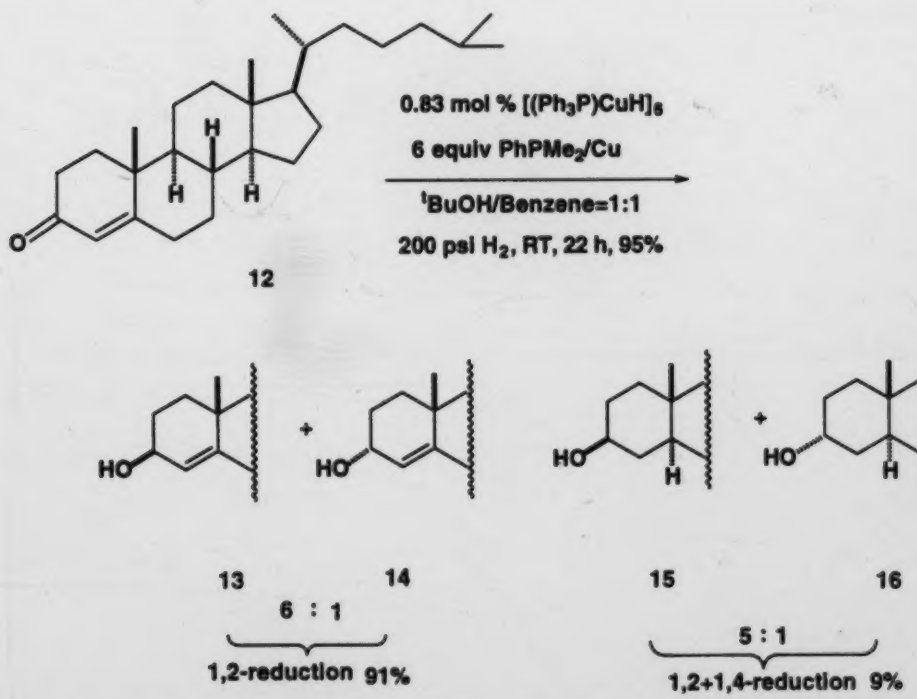
Scheme 18



When the reduction of 4-cholesten-3-one **12** was performed under 200 psi pressure of hydrogen at room temperature for 22 h, four products were obtained (**Scheme 19**), two major allylic alcohols (**13** and **14**, 91%) and two minor saturated alcohols (**15** and **16**, 9%). The two allylic alcohols were formed in a stereoisomeric ratio of 6 : 1, with the major product **13** (3β-OH) and minor isomer **14** (3α-OH). The two saturated alcohols were formed in a ratio of 5 : 1, consisting of a major diastereomer **15 trans** (3β-OH) and minor isomer **16 trans** (3α-OH). These products were identified individually by analysis and comparison of their spectroscopic data to those of authentic samples.[43,67,68] The product ratio was measured in the crude reaction mixture by

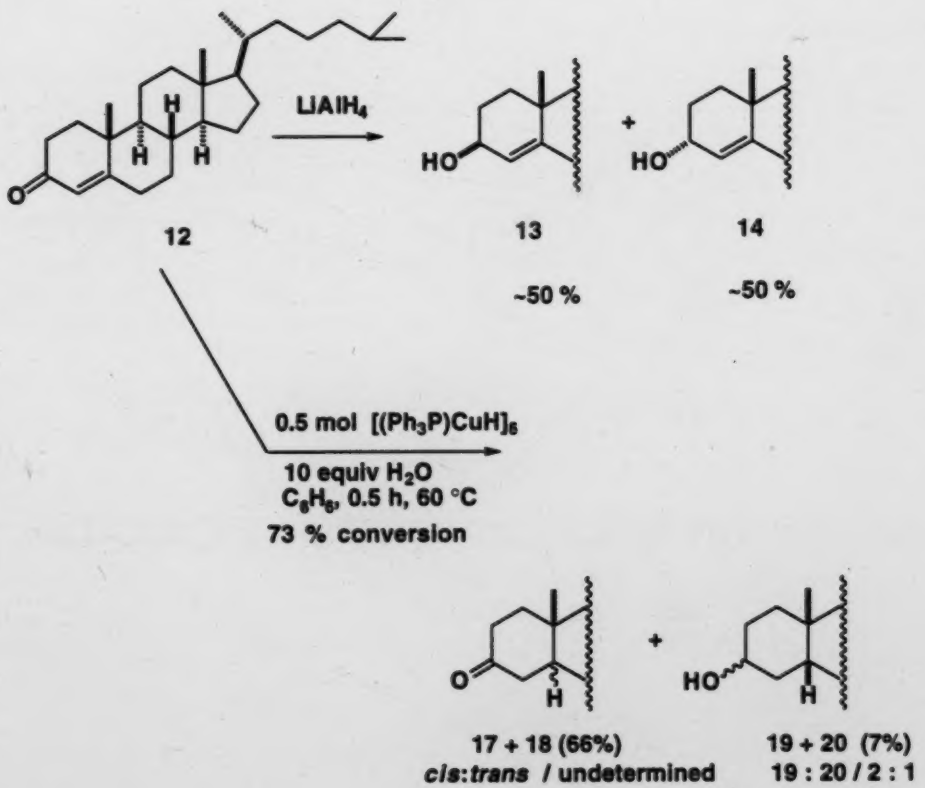
integration of the signals for the 3-methine protons in the ^1H NMR spectrum. The chracteristic signal for the 3-methine proton of the allylic alcohol **13** (3β-OH) appears as a multiplet at at δ 4.15 (m, 1 H), while the signal for the **14** (3α-OH) appears as a broad singlet at δ 4.07 (bs, 1 H). The olefin proton of the allylic alcohol **13** (3β-OH) appears as a broad singlet at δ 5.28 (bs, 1 H), and for **14** (3α-OH) the olefin proton signal appears as a doublet at δ 5.46 (d, J = 5.0 Hz, 1 H). For the two saturated alcohos **15** and **16**, the chracteristic signal for 3-methine proton of **15 trans** (3β–OH) appears as a triplet of tripletsg at δ 3.58 (tt, J = 4.9, 11.0 Hz, 1 H), while the signal for the **16 trans** (3α–OH) appears as a multiplet at δ 4.03 (m, 1 H). These assignments were double checked by using pyridine-d_5 as a NMR solvent instead of $CDCl_3$. When the same reaction was performed under 500 psi pressure of hydrogen, the reduction gave exactly the same result.

Scheme 19



For comparison, when 4-cholesten-3-one **12** is reduced with a stoichiometric amount of $LiAlH_4$, the two allylic alcohol **13** and **14** are obtained in a 1 : 1 ratio (**Scheme 20**).[68] In this case, our catalytic method gives a much better stereoselectivity of 6 : 1. When 4-cholesten-3-one **12** was reduced with stoichiometric amount of $[(Ph_3P)CuH]_6$ in the presence of water, the reaction gave the conjugate reduction products **17** and **18** as the major products along with a small amount of the cis–fused saturated alcohols **19** and **20** (**Scheme 20**).[43]

Scheme 20

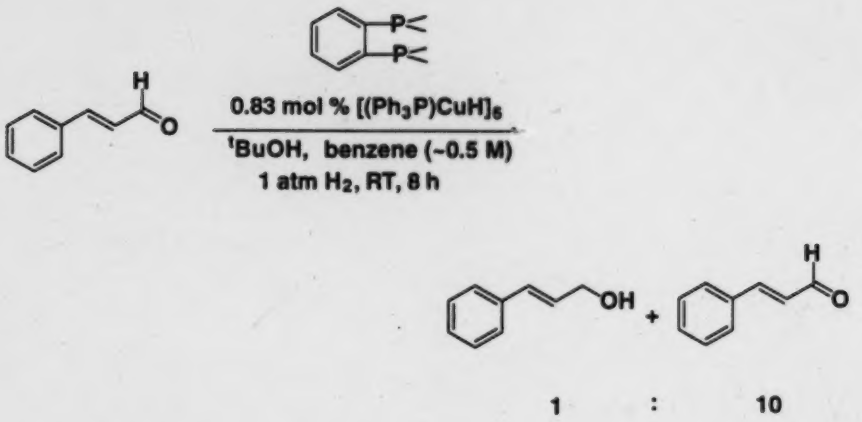


2. *Investigation of the Chemoselectivity and Catalytic Activity of New Catalysts.*

a. Bidendate phosphine catalysts.

In order to further improve the 1,2-selectivity of the catalytic hydrogenation, new hydridic copper (I) hydride catalysts were targeted. As discussed, there are two practical ways to make the copper(I) catalyst more hydridic: one option is to use more basic ancillary phosphine ligands, although such ligands may not necessarily stabilize the catalyst. A second possibility is to increase the number of phosphine centers coordinated to the metal. Bidendate phosphine ligands satisfy this latter criteria. In addition, when two phosphines are coordinated to the metal, more coordination sites at the metal will be blocked by the phosphine ligand. This can inhibit the carbon-carbon double bond of the α,β-unsaturated carbonyl compound from coordinating to the metal and direct the terminal carbonyl group to coordinate preferentially. Such catalysts should in principle give better 1,2-selectivity.

Based on the above analysis and the success of dimethylphenylphosphine ligand, 1,2-bis(dimethylphosphino)benzene was tested first. Thus, a benzene solution of *trans*-cinnamaldehyde was combined with a benzene solution of catalytic amount of $(Ph_3P)CuH]_6$, 2 equivalents/Cu of 1,2-bis(dimethylphosphine)benzene, 40 equivalents/Cu of *tert*-butanol. The resulting solution was hydrogenated under one atmosphere pressure of hydrogen for 8 h. Analysis of the crude mixture by ^1H NMR spectroscopy showed the presence of starting material and allylic alcohol in a ratio of 10 : 1, and no saturated alcohol product was observed (**eq. 13**).



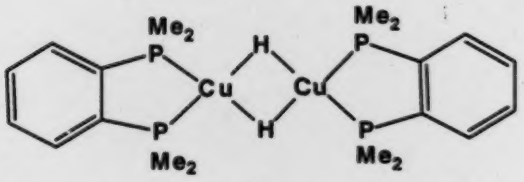
eq. 13

When the same hydrogenation was performed under 500 psi pressure of hydrogen for 44 h, the reaction still did not go to completion. The crude ^{1}H NMR spectrum showed the presence of starting material and the allylic alcohol in a ratio of 1.7 : 1; only a trace amount of saturated alcohol product was detected. Using the same catalyst system, R-(-)carvone was hydrogenated under one atmosphere pressure of hydrogen for 3 days, but no allylic alcohol and saturated alcohol products were observed.

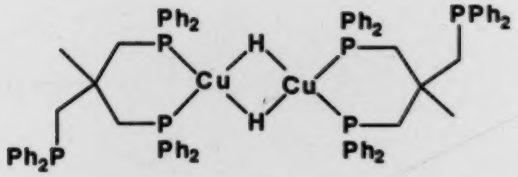
To investigate the structure of the new catalyst, $[(Ph_3P)CuH]_6$ and 1,2-bis (dimethylphosphine)benzene were mixed in deuterated benzene in a 1 : 1 ratio based on copper content. The resulting solution was shaken for several minutes and then placed in a NMR tube for ^{1}H NMR analysis. The ^{1}H NMR spectrum showed that the hydride signal in $[(Ph_3P)CuH]_6$ (δ = 3.52, br. septet) had disappeared. A new broad singlet appeared at high field (δ = 1.25, br s), which is probably the new hydride signal, reflecting a sharp increase in hydridic character. For comparison, in the tripod copper(I) hydride complex **21**, the hydride signal appears at δ = 1.83 in the ^{1}H NMR spectrum. Further evidence for the formation of a new hydride complex is the color change. When $[(Ph_3P)CuH]_6$ and 1,2-bis(dimethylphosphine)benzene are mixed in benzene, the solution color changes from red to orange-yellow (homogeneous). When

dimethylphenylphosphine is mixed with $[(Ph_3P)CuH]_6$, the solution color also changes from red to orange-yellow (homogeneous). Such a color change indicates that the red $[(Ph_3P)CuH]_6$ hexamer is dissociated and new copper(I) complex are formed. Based on the low catalytic activity and the ^1H NMR spectrum analysis, we speculate that the new copper(I) complex **21** has a dimeric structure, similar to the tripod copper(I) hydride complex **1** (**Scheme 21**).

Scheme 21



21



1

In the dimer **21**, the hydride forms bridged bonds between two copper atoms, and each copper has two coordinated phosphine moieties. It is likely that such a dimer is more thermally stable than the dimethylphenylphosphine copper(I) hydride catalyst system especially toward phosphine dissociation, therefore, it gives low catalytic activity.

The second bidendate phosphine examined was 1,2-bis(dimethylphosphino)ethane (DMPE, commercially available). The purpose for selecting this more basic trialkyl phosphine ligand was to make a more hydridic copper(I)

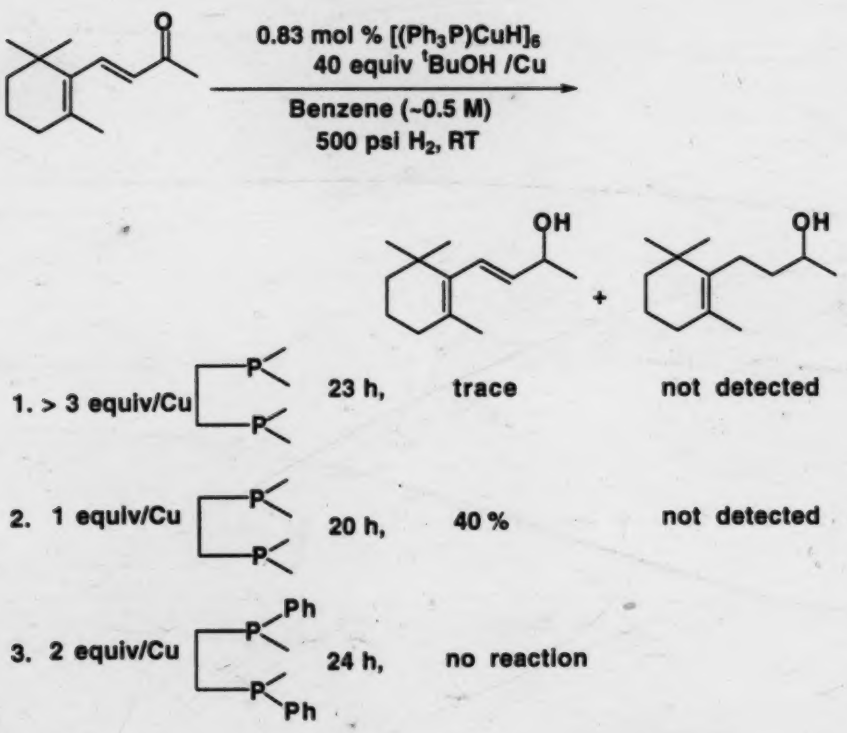
hydride catalyst, which might be less thermally stable than the dimer **21** and more reactive toward 1,2-reduction. Thus, the reduction of β-ionone was tested using the DMPE–derived copper(I) hydride catalyst system. When more than three equivalents/Cu of DMPE was used, the reduction only gave a trace amount of allylic alcohol product after the substrate was hydrogenated under 500 psi pressure of hydrogen for 23 h (**Scheme 22, entry 1**). When only one equivalent/Cu of DMPE was used, under otherwise similar conditions, the reduction proceeded to give 40% allylic alcohol product, with no saturated alcohol product observed (**Scheme 22, entry 2**). To investigate the catalyst formation, in a separate experiment, 6 equivalents/Cu of DMPE was mixed with $[(Ph_3P)CuH]_6$ in benzene under nitrogen. The resulting brown solution was maintained at room temperature for 3 h, during which time the solution turned dark and a small amount of black precipitate(presumably Cu(0)) was produced in the solution, indicating the catalyst was decomposing.

Finally, the 1,2-bis(phenylmethylphosphino)ethane ligand was tested. There are several reported methods for the synthesis of this phosphine compound.[69,70] We found that it is very difficult to get the pure product using Brooks' method, so we prepared the compound by Chou's method.[70] Using a catalytic amount of $[(Ph_3P)CuH]_6$, 2 equivalents/Cu of 1,2-bis(phenylmethylphosphine)ethane, 40 equivalents/Cu of *tert*-butanol, β-ionone was hydrogenated under 500 psi pressure of hydrogen for 24 h. The crude ^1H NMR spectrum showed that no alcohol products were formed (**Scheme 22, entry 3**).

The above results demonstrate that bidendate phosphine ancillary ligands do not form efficient catalysts for the 1,2-reduction of α,β-unsaturated carbonyl compounds. One possible reason is that such phosphine ligand coordinated to copper(I) hydride form catalysts that are too stable, due to the formation of the dimer as depicted in **Scheme 21**. Another possible reason is that some bidendate trialkyl phosphine ancillary ligands

are too basic, resulting the catalyst decomposition by reduction of the metal to Cu(0). Also, it is possible that the active catalyst has only one phosphine ligand on the metal; the bidendate phosphine would then inhibit the formation of such an active catalyst. The less basic and larger tripod ligand might dissociate a second phosphine arm better to form such active catalyst.

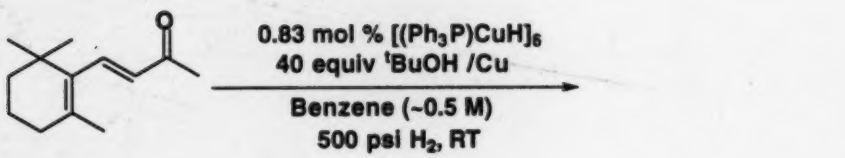
Scheme 22



b. Common tertiary phosphine catalysts.

In order to find a good catalyst which is both reasonably stable and highly selective, some common tertiary phosphines were also screened. Using a catalytic amount of $[(Ph_3P)CuH]_6$, 6 equivalents/Cu of tricyclohexylphosphine, 40 equivalents/Cu of *tert*-butanol, β-ionone was hydrogenated under 500 psi pressure of hydrogen for 20 h. Unfortunately the reaction only gave 5 % saturated alcohol product (**Scheme 23, entry 1**). When tri-n-butylphosphine was used as the added phosphine, under similar conditions, the reduction reaction showed complete conversion after 18 h, giving the allylic alcohol as the major product (**Scheme 23, entry 2**).

Scheme 23

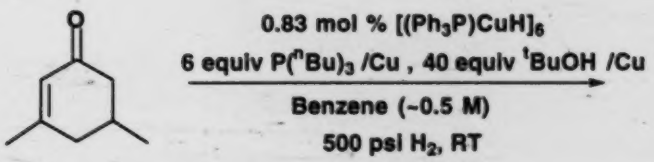


1. 6 equiv/Cu	$P(Cy)_3$	20 h,	trace	5 %
2. 6 equiv/Cu	$P(^nBu)_3$	18 h,	79 %	21 %

From the above reaction we found that the tri-n-butylphosphine ancillary ligand showed good activity and moderate selectivity. To test the generality of this ligand, a cyclic substrate, 3,5-dimethylcyclohexenone was hydrogenated. Using the same

conditions, the reduction reaction was performed under 500 psi pressure of hydrogen for 18 h. The crude ^{1}H NMR spectrum showed complete conversion. The allylic alcohol and saturated alcohol, however, were formed in a ratio of only 1 : 5. The allylic alcohol consisted of two isomers, trans OH : cis OH = 75 : 25. The saturated alcohol also consisted of two isomers, trans OH : cis OH = 53 : 47 (**Scheme 24**). All of the products were identified by comparison of their ^{1}H NMR spectra to those of authentic samples and by evaluation of the observed coupling constants.

Scheme 24



trans OH:cis OH = 75:25. trans OH:cis OH = 53:47

1 : 5

When triisopropylphosphine and triethylphosphine were tested under the same reaction conditions, no alcohol products were produced. Previous experiments in our group also found that trialkylphosphines, such as trimethylphosphine and triethylphosphine, etc., did not generate active catalysts for enone reduction when these phosphines were mixed with $[(Ph_3P)CuH]_6$. This is probably because trialkyphosphines are too basic and can not form thermally stable copper(I) alkoxides at room temperature.

c. Phenyl–substituted cyclic phosphine catalysts.

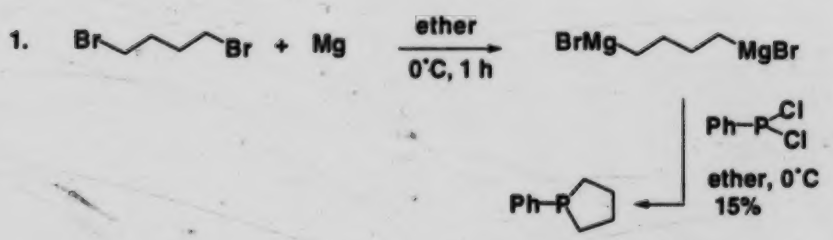
Previous investigation in our group has found that the diethylphenylphosphine–derived copper(I) hydride catalyst shows very low activity for the reduction of ketones,[43] but the dimethylphenylphosphine analogue, as we have seen, gives good activity and selectivity. It was interesting, therefore, to know what kind of catalyst would be obtained when the two terminal methyl groups in the diethylphenylphosphine are bonded together to form a phenylphospholane ligand, which is more sterically compact than the diethylphenylphosphine ligand. If the phenylphospholane ligand generates a good catalyst, the phospholane backbone can be developed into chiral cyclic phosphine compounds, which are promising ligands for asymmetric catalysis. For example, (S, S)-2,5-dimethyl-1-phenylphospholane, made by Burk's method,[71] forms an interesting cationic complex with rhodium,[72,73] which is an efficient catalyst for the enantioselective hydrogenation of some unsaturated organic substrates.[71]

Our investigation started from the synthesis of the simple unsubstituted 1-phenylphospholane, which was expected to provide some basic data and determine whether this phospholane is a better ligand than diethylphenylphosphine and if the cyclic phosphine template is a good ligand type for copper(I) hydride catalysts.

There are several methods available to prepare the 1-phenylphospholane. The most straightforward one was reported by Gruttner (**Scheme 25, entry 1**),[74] in which the 1-phenylphospholane is made by the reaction of 1,4-bis(bromomagnesium)butane and dichlorophenylphosphine. The synthesis is simple but the product isolation and purification are difficult. The ^{1}H NMR spectrum showed that the product made by this method was not pure and attempts to purify the product were unsuccessful. The

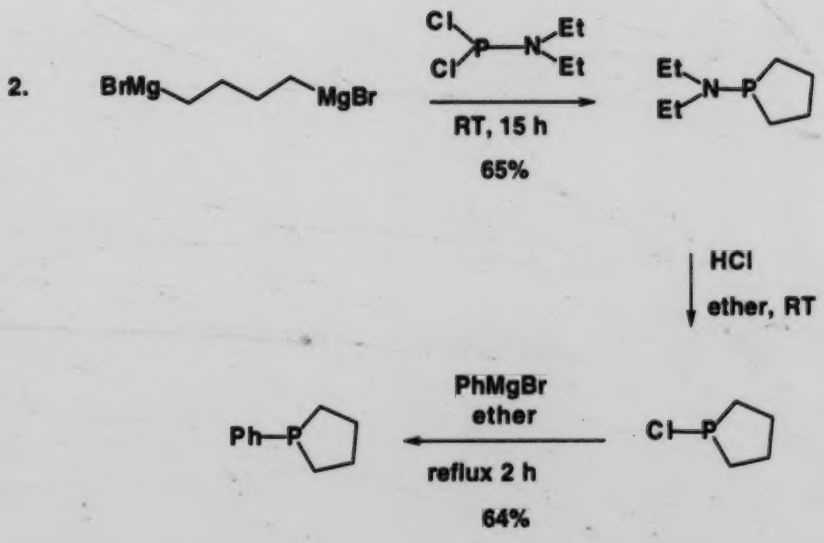
litrature did not provide ^1H NMR data, so it is difficult to assess the purity of the product obtained by Gruttner.

Scheme 25



Gruttner, G.; Krause, E.

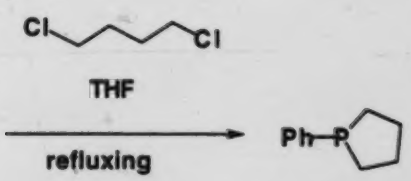
Chem. Ber. **1916**, *49*, 437.



Fell, H.; Bahrmann, H.

Synthesis **1974**, 119.

3. $PhPCl_2 + Li \xrightarrow[\text{refluxing}\\ \text{12 h}]{\text{THF}} PhPLi_2$



2 h, 29%

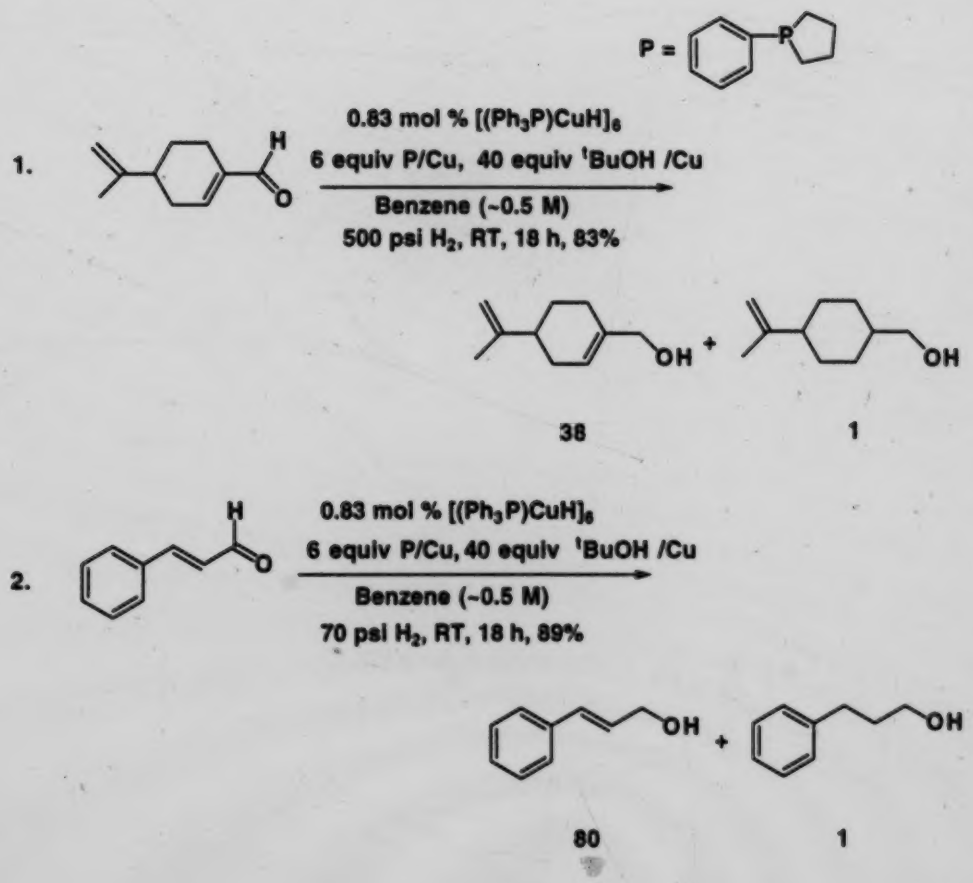
Issleib, K.; Hausler, S.

Chem. Ber. **1961**, *94*, 113.

The second method for the synthesis of 1-phenylphospholane was reported by Fell and Bahrmann (**Scheme 25, entry 2**).[75] However, this four step synthesis also did not give pure 1-phenylphospholane after the product was separated by inert atmosphere flash column chromatography and two distillations. Finally, we synthesized 1-phenylphospholane by the reaction of 1,4-dichlorobutane and $PhPLi_2$ (**Scheme 25, entry 3**). The method is basically the same as Issleib's method[76] with some experimental modification, and give the phosphine in high purity, but only in 10% overall yield.

The reduction of α,β-unsaturated aldehyde substrates using the 1-phenylphospholane derived copper(I) hydride catalyst system showed excellent 1,2-selectivity. The selectivity observed *is even better* than the selectivity of the dimethylphenylphosphine derived catalyst system. For the reduction of perillaldehyde, for example, the reaction was performed under 500 psi pressure of hydrogen for 18 h and produced the allylic alcohol and the saturated alcohol products in a ratio of 38 : 1 (**Scheme 26, entry 1**).

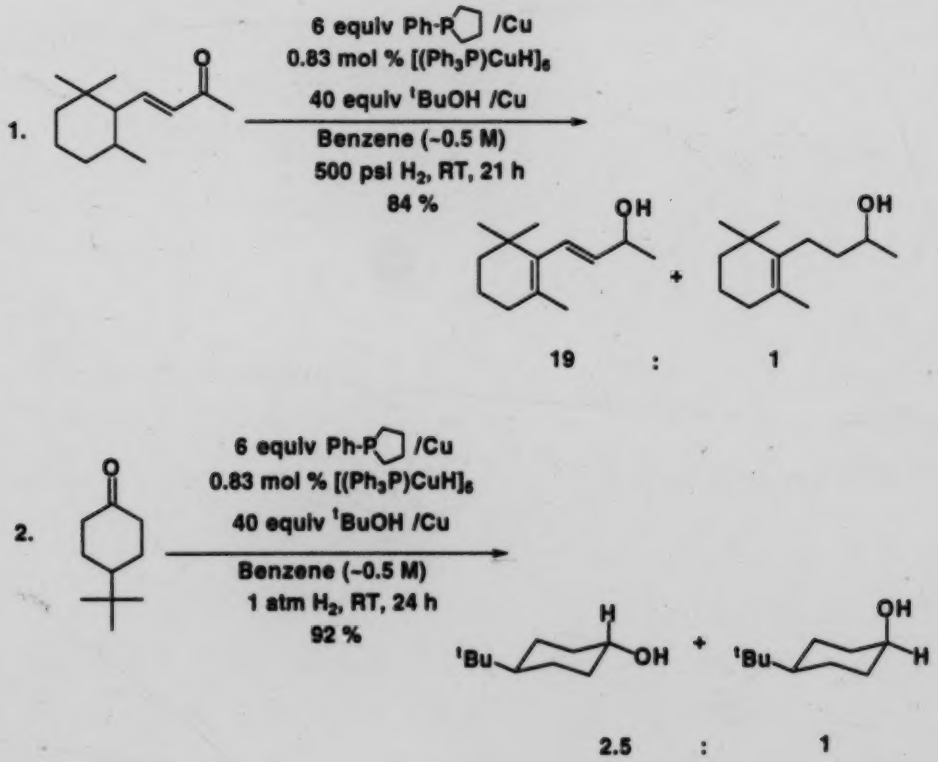
Scheme 26



For the reduction of *trans*-cinnamaldehyde, the reaction was performed under 70 psi pressure of hydrogen for 18 h. It produced the allylic alcohol and saturated alcohol products in a ratio of 80 : 1. Both reactions gave good yields.

Using the 1-phenylphospholane–derived copper(I) hydride catalyst system, under 500 psi pressure of hydrogen, the reduction of β-ionone showed complete conversion after 21 h and the allylic alcohol and saturated alcohol products were obtained in a ratio of 19 : 1 (**Scheme 27, entry 1**), slightly lower selectivity than obtained using dimethylphenylphosphine–derived copper(I) hydride catalyst system.

Scheme 27



A simple ketone substrate, 4-*tert*-butylcyclohexanone, was also tested using the 1-phenylphospholane–derived copper(I) hydride catalyst system. The reduction was performed under one atmosphere pressure of hydrogen for 24 h and the crude mixture ^{1}H NMR showed complete conversion. The *trans*-4-*tert*-butylcyclohexan-1-ol and *cis*-4-*tert*-butylcyclohexan-1-ol products were formed in a ratio of 2.5 : 1, indicating the hydride favors axial addition to this ring system. Under the same reaction conditions, the dimethylphenylphosphine–derived catalyst gives the two alcohol products in a similar ratio of 2 : 1.[43] These results demonstrate that the 1-phenylphospholane–derived catalyst is highly selective.

For the reduction of simple cyclic conjugated enone substrates, however, this catalyst system still does not give improved 1,2-selectivity. For example, when the 3,5-dimethylcyclohexenone was hydrogenated under 500 psi of hydrogen for 20 h, the allylic alcohol and the saturated alcohol products were formed, but in a ratio of only 1 : 2.

d. Racemic alkylmethylphenylphosphine catalysts.

Further investigation of the catalyst ligand was focused on alkylmethylphenylphosphines. From our previous research on phosphine ligands, we found that the selectivity and catalytic activity of the catalyst is very sensitive to the structure of phosphine compounds and there is no mature theory that can direct us to the best ligand. Based on the fact that the dimethylphenylphosphine is a good ligand, we attempted to replace one of the methyl group with an other alkyl group such as ethyl, propyl, and even cyclohexyl, to see whether such modification would improve the selectivity and catalytic activity of the new phosphine–coordinated copper(I) hydride catalyst. Such investigation would also provide more information on the ligand structure-catalyst activity relationships. Another important goal of this modification is that such phosphines are chiral, and the nonracemic chiral phosphines could be used in future catalytic asymmetric hydrogenation. In early investigations, enantiomerically pure alkylmethylphenylphosphines were used for the preparation of asymmetric hydrogenation catalysts.[77-80] For example, Knowles made the asymmetric catalyst trichlorotris(methylphenylpropylphosphine)rhodium by treating optically active (-)-methylphenylpropylphosphine with rhodium trichloride trihydrate. This catalyst was used for the asymmetric hydrogenation of α-phenylacrylic acid.[81]

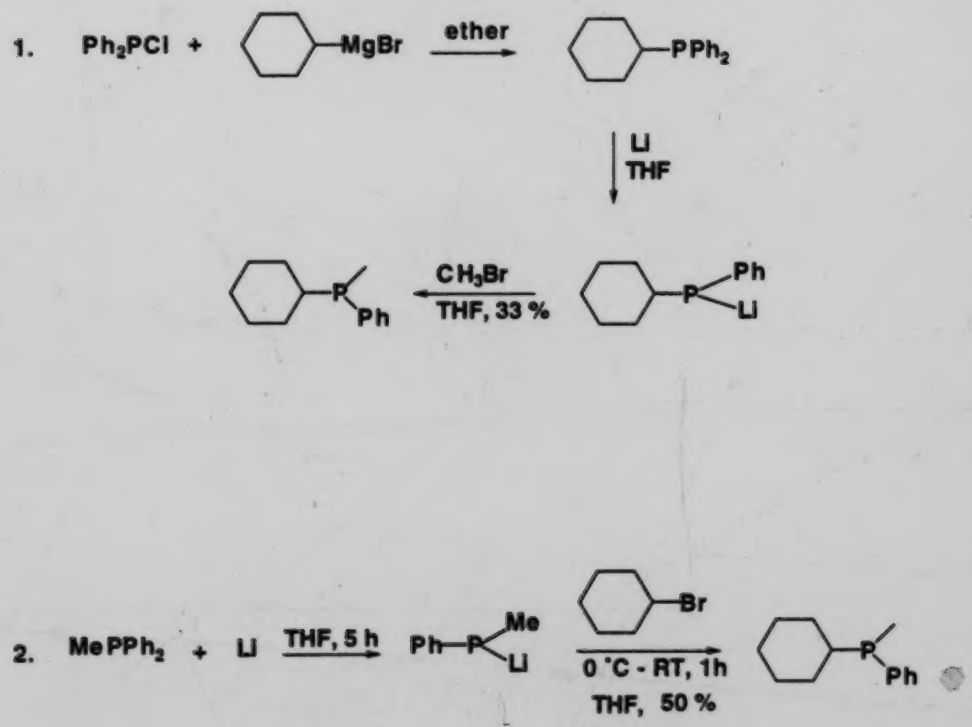
Our initial investigation started from the *racemic* alkylmethylphenylphosphine–derived copper(I) hydride catalysts because the racemic phosphines are easy to make and

inexpensive. The investigation of the racemic phosphine–derived catalysts provides some basic data, such as chemoselectivity and catalytic activity, from which we can decide whether the phosphine must be further modified or directly developed into the corresponding resolved phosphines for asymmetric hydrogenation.

Ethylmethylphenylphosphine and methylphenylpropylphosphine were prepared by the reported method.[82] For the synthesis of cyclohexylmethylphenylphosphine, the literature method calls for the following synthesis route (**Scheme 28, entry 1**). In the first step, chlorodiphenylphosphine is treated with the cyclohexyl Grignard reagent in dry ether to form diphenylcyclohexylphosphine. Subsequent treatment of diphenylcyclohexylphosphine with lithium affords the phenylcyclohexylphosphide anion, which is treated with methyl bromide to yield the racemic cyclohexylmethylphenylphosphine. Because we had already access to methyldiphenylphosphine instead of chlorodiphenylphosphine, we synthesized the cyclohexylmethylphenylphosphine by a different but equally simple route (**Scheme 28, entry 2**). Thus, methyldiphenylphosphine was treated with lithium metal to produce the phenylmethylphosphide anion, which was treated with cyclohexyl bromide to afford the recemic cyclohexylmethylphenylphosphine in reasonable yield. The product was purified by distillation (135 °C/5 torr) followed by inert atmosphere flash column chromatography. The spectroscopic data of the product were identical to that of the reported compound.[82]

With these alkylmethylphenylphosphine compounds in hand, the reduction of organic substrates was undertaken. Since we had already found two excellent catalyst systems (the dimethylphenylphosphine and 1-phenylphospholane–derived copper(I) hydrides, (*vide supra*) for the reduction of the α,β-unsaturated aldehydes, continued investigation was focused on the catalytic reduction of α,β-unsaturated ketones using the new phosphine–derived catalysts.

Scheme 28

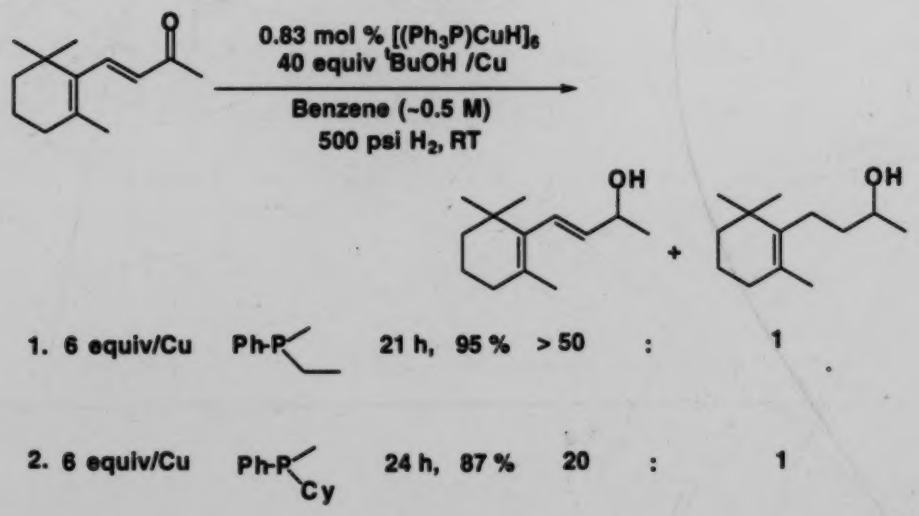


When a solution of β-ionone and the ethylmethylphenylphosphine–derived copper(I) hydride catalyst system was hydrogenated under 500 psi pressure of hydrogen for 21 h, the reaction showed complete conversion to two alcohol products, obtained in a 95 % combined yield. The allylic alcohol and the saturated alcohol products were formed in a ratio of more than 50 : 1 (**Scheme 29, entry 1**). When the ethylmethylphenylphosphine was replaced by cyclohexylmethylphenylphosphine, under otherwise the similar conditions, the reaction gave a 87 % yield of the same products. The allylic alcohol and saturated alcohol products were formed in a ratio of 20 : 1 (**Scheme 29, entry 2**). These experimental results demonstrate that the dimethylphenylphosphine template is not required for chemoselective 1,2-reduction of α,β-

unsaturated carbonyl compounds. One of the methyl groups can be replaced by another alkyl group.

Based on the fact that dimethylphenylphosphine is a good ligand, diethylphenylphosphine is very poor, and ethylmethylphenylphosphine is a little better than dimethylphenylphosphine, it is evident that even a small variation in the phosphine structure dramatically changes the catalyst activity. This phenomenon is both interesting and very hard to explain. The good activity and selectivity obtained from the cyclohexylmethylphenylphosphine derived catalyst system indicates that the scope for the modification of one of the methyl groups in dimethylphenylphosphine is potentially broad, and the results also provide some promising leads for asymmetric hydrogenation of α,β-unsaturated carbonyl compounds using chiral alkylmethylphenylphosphines.

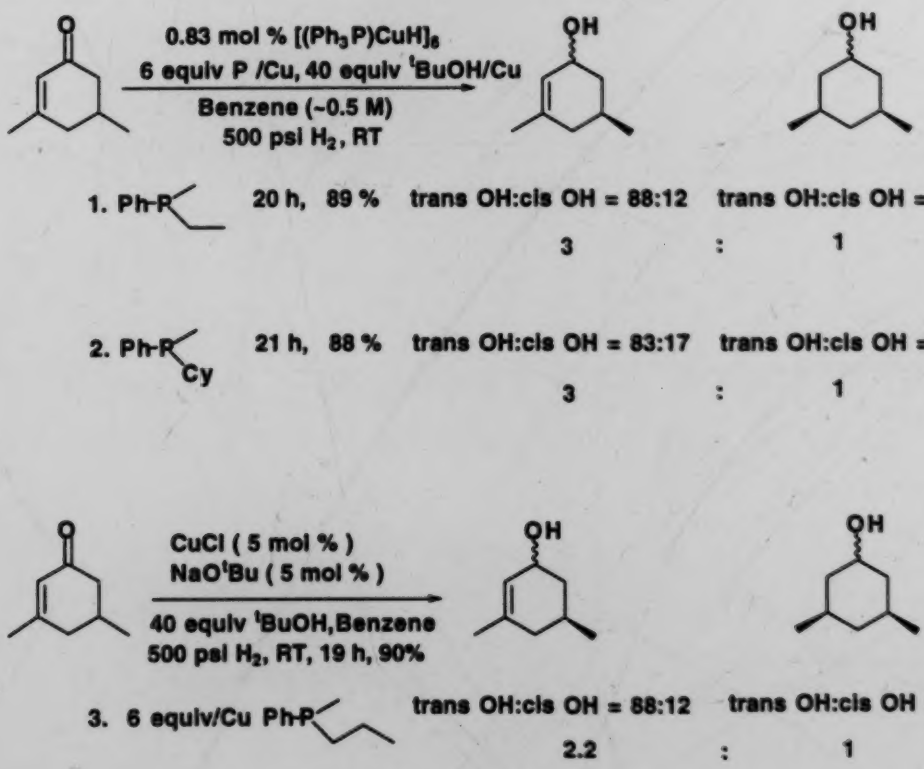
Scheme 29



For the reduction of simple cyclic enone substrates, however, the alkylmethylphenylphosphines still do not give improved selectivity. The reduction of 3,5-dimethylcyclohexenone using the ethylmethylphenylphosphine–derived catalyst

system gave the allylic alcohol and saturated alcohol in a ratio of 3 : 1. The two allylic alcohol steroisomers were formed in a ratio of 88 : 12, and the two saturated alcohol stereoisomers were formed in a nonselective ratio of 42 : 58 (**Scheme 30, entry 1**). When the same substrate was reduced by the cyclohexylmethylphenylphosphine–derived catalyst system under otherwise the same reaction conditions, it gave very similar results (**Scheme 30, entry 2**).

Scheme 30



In an attempt to improve the 1,2-selectivity, complete removal of the triphenylphosphine from the reduction medium was achieved by generating the catalyst from a simple copper(I) salt. Thus, the methylphenylpropylphosphine–coordinated

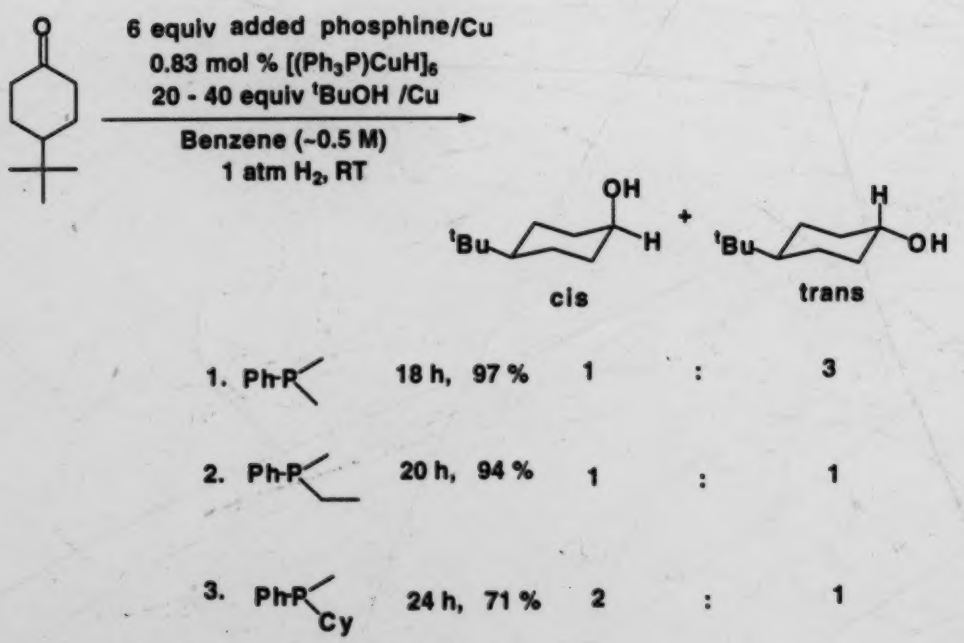
copper(I) catalyst was made by the reaction of CuCl and NaO^tBu in the presence of methylphenylpropylphosphine. When 3,5-dimethylcyclohexenone was reduced with this catalyst system under 500 psi pressure of hydrogen for 19 h, the reaction did not give improved selectivity (**Scheme 30, entry 3**). The new catalyst system showed almost the same selectivity as the ethylmethylphenylphosphine and $[(Ph_3P)CuH]_6$–derived catalyst systems did.

In order to test the stereoselectivity of the alkylmethylphenylphosphine–derived catalyst system for the reduction of simple cyclic ketones, the reduction of 4-*tert*-butylcyclohexanone was investigated. The reaction was performed under atmospheric pressure of hydrogen at room temperature and the reaction results are presented in **Scheme 31**. The results show that when the alkyl group of the alkylmethylphenylphosphine ligand is enlarged, the ratio of *cis*-4-*tert*-butylcyclohexan-1-ol to *trans*-4-*tert*-butylcyclohexan-1-ol is increased. The dimethylphenylphosphine gave a 1 : 3 ratio (**Scheme 31, entry 1**), the ethylmethylphenylphosphine gave a 1 : 1 ratio (**entry 2**), and the cyclohexylmethylphenylphosphine gave a 2 : 1 ratio (**entry 3**). These experiments demonstrate that the larger phosphine–coordinated copper(I) hydride reagents favor equatorial hydride delivery while the small phosphine coordinated copper(I) hydride reagents favor axial hydride delivery, similar to the selectivities observed using classical stoichiometric hydride reagents.[83]

The above experiments also demonstrate that when the alkyl group of the alkylmethylphenylphosphine ligands is enlarged, the activity of the corresponding catalyst is decreased. Under one atmosphere of hydrogen, the reduction of 4-*tert*-butylcyclohexanone using dimethylphenylphosphine–derived catalyst gave 97% yield after 18 h, the ethylmethylphenylphosphine–derived catalyst gave 94 % yield after 20 h, and the cyclohexylmethylphenylphosphine–derived catalyst gave only 71% conversion after 24 h (**Scheme 31**). These results suggest that the large alkyl groups in the

alkylmethylphenylphosphine ligand inhibit the hydride transfer to the 4-*tert*-butylcyclohexanone.

Scheme 31

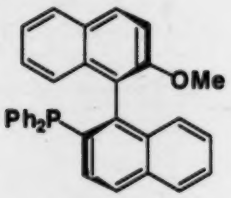


e. Racemic binaphthyldimethylphosphine catalysts.

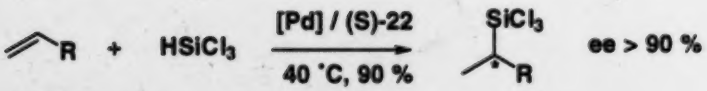
In order to find new phosphine ligand templates for selective 1,2-reduction of α,β-unsaturated carbonyl compounds and also for development of asymmetric hydrogenation catalysts, the ligand screening was extended to binaphthyldimethylphosphine-type ligands. It was anticipated that the coordination of the large binaphthyl moiety will results in a more hindered copper(I) hydride complex, inhibiting carbon-carbon double bond of the α,β-unsaturated ketone from coordinating to

the copper, so that only the terminal carbonyl group could react with the copper. Such coordination should give good 1,2-selectivity. Such phosphine ligands are also chiral and have potential to generate various asymmetric catalysts. For example, the monodentate optical phosphine (MOP) (S)-**22** has been synthesized and used for the enantioselective hydrosilylation of 1-alkenes (**Scheme 32**).[84]

Scheme 32



22



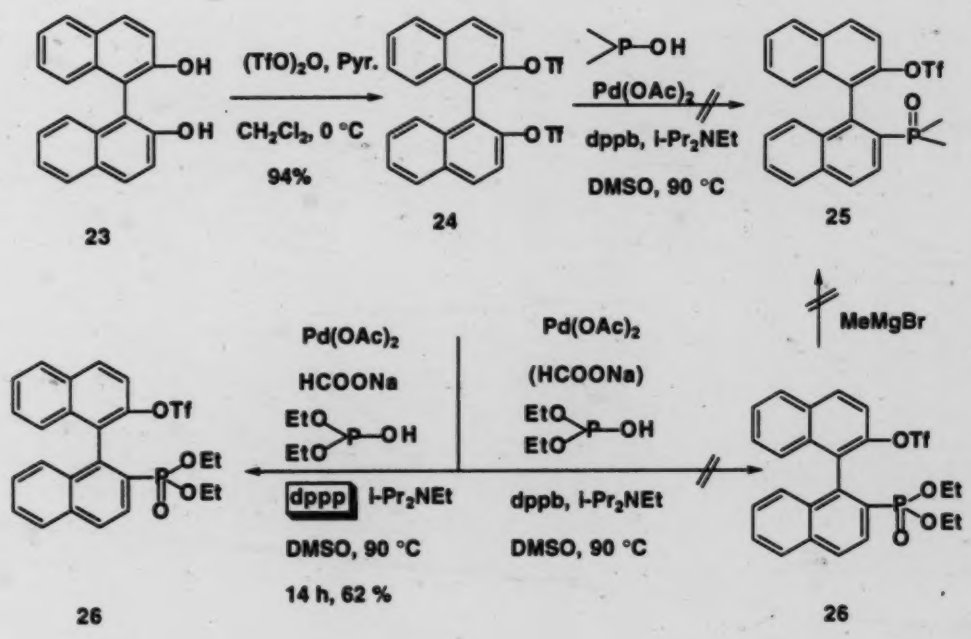
Most reported "MOP's" are triarylphosphines;[85-87] such phosphines are air stable and easy to make. The dialkylbinaphthyl MOPs are unknown. This type of phosphine is much more basic than the triaryl MOP's and must prepared and stored in the absence of oxygen. The synthesis of dialkylaryl MOP's provide new ligand systems for both copper hydride research and for other asymmetric catalysis research.

Our initial investigation was focused on the synthesis of racemic dialkylaryl MOP compounds. Thus, treatment of racemic 1,1'-bis(naphthol) **23** with trifluoromethanesulfonic anhydride in pyridine afforded 2,2'-bis-(trifloromethanesulfonyloxy)-1,1'-binaphthyl **24** in 94 % yield (**Scheme 33**). This procedure was based on Uozumi's method[85] with slight modifications in the reaction time and purification process. Attempts to make the 2-dimethylphosphinyl-2'-

trifloromethanesulfonyloxy-1,1'-binaphthyl **25** by using Hayashi's method[84] were not successful, although the method gives high yields in the synthesis of the triaryl MOP, 2-diphenylphosphinyl-2'-trifloromethanesulfonyloxy-1,1'-binaphthyl.

Another attempt to make compound **25** proceeded by way of compound diethylphosphinite **26**, because we speculated that this compound could be converted to phosphine oxide **25** by methylation. After investigating several different reaction systems, compound **26** was prepared by the procedure shown; however, the conversion of **26** to **25** was found to be impossible (**Scheme 33**). Therefore, we re-investigated the conversion from **24** to **25** using direct methods.

Scheme 33



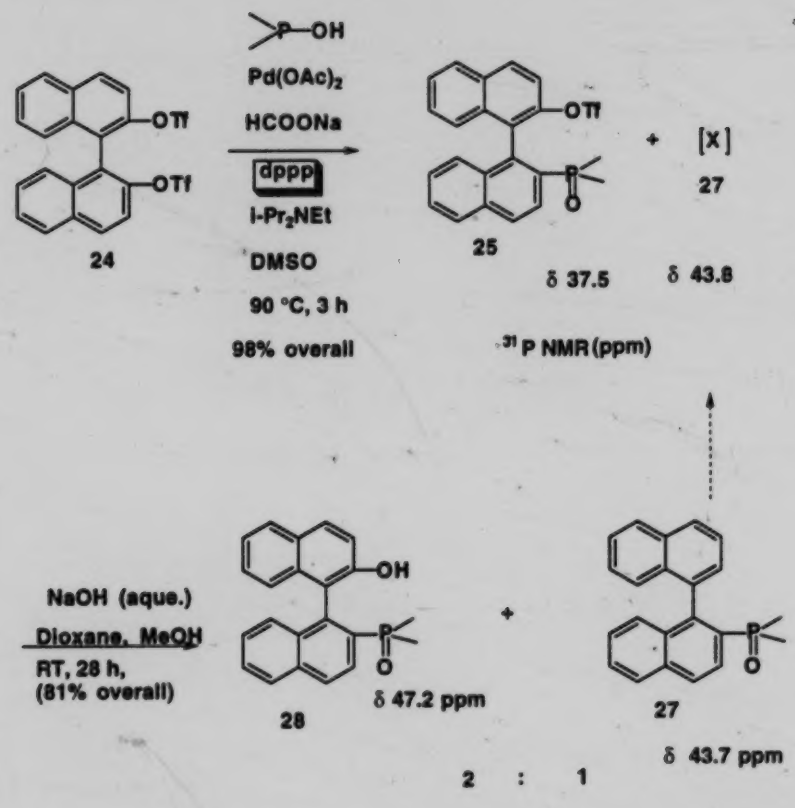
After investigating many different reaction conditions, the direct conversion of **24** to **25** was finally accomplished. Thus, treatment of **24** with dimethylphosphine oxide in the presence of diisopropylethylamine, sodium formate, catalytic palladium (II) acetate,

and 1,3-bis(diphenylphosphino)propane (dppp) gave compound **25** along with an unknown byproduct, compound **27**. Although the two products can not be separated by flash column chromatography and TLC analysis only showed a single spot; the ^{31}P NMR spectrum clearly shows two resonance at δ 43.8 and 37.5 ppm, indicating the presence of two different phosphines. Without separation, the mixture of **25** and **27** was hydrolyzed with aqueous sodium hydroxide, giving two products **28** and **27** in a ratio of 2 :1 (**Scheme 34**). At this stage, the two products can be separated very conveniently by chromatography. Because the spectroscopic data for compound **27** obtained in this step is also found in the ^{1}H NMR spectrum obtained in the previous step, it is clear that the byproduct is formed by the reduction of the remaining triflate substituent under the cross coupling reaction conditions.

Both products (**27** and **28**) are potentially useful ligand types, so the two separated products were each carried on to the final phosphine products. Reduction of the phosphine oxide **27** with trichlorosilane and triethylamine in xylene at reflux led to desired phosphine product **31**. Compound **31** was separated and purified by inert atmosphere flash column chromatography because it is air sensitive. In an open solution, compound **31** is oxidized back to compound **27** within an hour (**Scheme 35**).

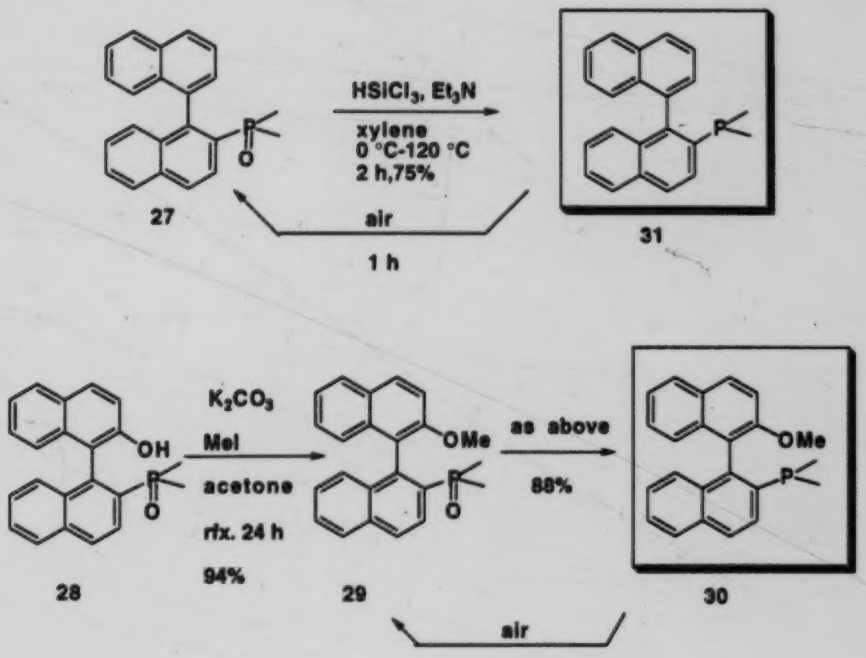
Treatment of hydroxy compound **28** with methyl iodide in the presence of potassium carbonate in acetone afforded compound **29** nearly quantitatively, which was subsequently reduced to compound **30** by the same method used in the reduction of compound **27** to **31**.

Scheme 34



From the above synthesis, two different racemic binaphthyldimethylphosphine ligands were obtained. However, neither of these two phosphine ligands produce copper(I) hydride catalysts that are active for the reduction of enones and ketones. For example, the reduction of 4-*tert*-butylcyclohexanone using compound **30** and $[(Ph_3P)CuH]_6$ under 1000 psi of hydrogen only gave 13 % *cis*-4-*tert*-butylcyclohexan-1-ol; under similar conditions, the reduction of ***trans***-4-phenyl-3-buten-2-one resulted in absolutely no reaction. One possible reason for this lack of reactivity is that such a ligand (or two) coordinated to the copper(I) hydride catalyst may make a catalyst that is too sterically hindered to coordinate with the substrate.

Scheme 35



D. Conclusions

Chemoselective catalytic hydrogenation of α,β-unsaturated aldehydes and ketones using phosphine stabilized Cu(I) hydride complexes has been investigated. The results demonstrate that dimethylphenylphosphine and 1-phenylphospholane derived catalyst systems give excellent 1,2-selectivity for the reduction of α,β-unsaturated aldehydes and ketones except for the reduction of some simple cyclic conjugated enones. The bidendate phosphines, trialkylphosphines, and binaphthyldimethylphosphines do not generate selective and active copper(I) hydride catalysts. However, the racemic alkylmethylphenylphosphine derived catalyst series show very good selectivity and

catalytic activity. Such phosphine ligands can be made in enantiomerically resolved form to generate asymmetric copper(I) hydride catalysts. The investigation revealed some interesting relationships between phosphine structure and catalyst activity, but it is very difficult to rationalize the subtle steric and electronic effects that clearly came into play during the hydrogenation process.

II. PART TWO

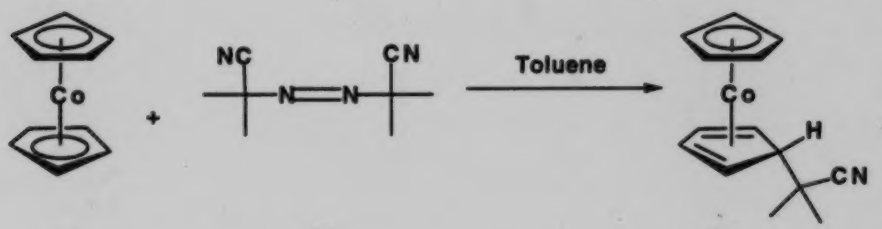
FREE RADICAL ALKYLATION OF TITANIUM(III) ALLYL AND PROPARGYL COMPLEXES.

A Introduction and Historical Perspective

Free radicals are important intermediates in many organic reactions. Their application in organic synthesis, especially for the preparation of synthetically interesting molecules, was limited before the 1980's, mainly because of low selectivity.[88-90] Since then, developments have been concentrated on new methodologies with good selectivity and applications in organic synthesis. It is now clear that free radical reactions have become important synthetic strategies in organic chemistry. Among various radical reactions, metal-directed free radical reactions are also very interesting and may become important, because such reactions usually show unique selectivity and reactivity.

1. *Free Radical Addition Reactions of Transition Metal Allyl Complexes*

The first direct investigation of the addition of organic radicals to an organometallic hydrocarbyl ligand was reported in 1970 by Herberich and Schwarzer.[91] In this study, they found direct proof of the addition of a free radical to the nineteen electron cobaltocene complex **32**. Thermal decomposition of an excess of azoisobutyronitrile (AIBN) in boiling toluene containing complex **32** affords cyclopentadienyl-[5-exo-(1-cyano-1-methylenyl)cyclopentadiene]cobalt **34** almost quantitatively (**eq. 14**).

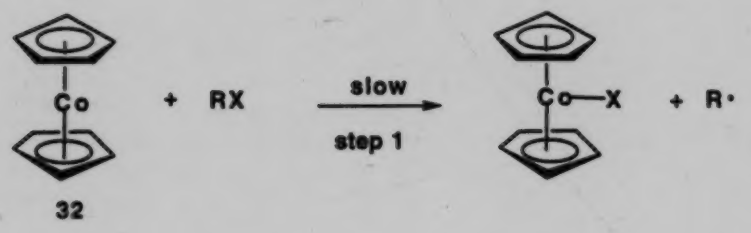


32 **33** **34**

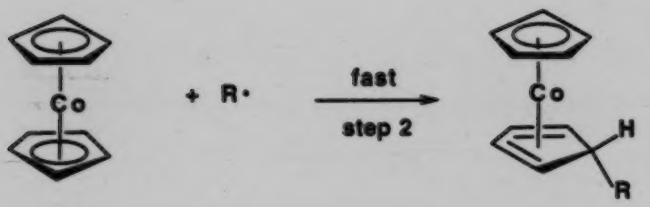
eq. 14

Actually, in 1969 Herberich and Bauer [92] had already proposed a two step radical mechanism for the reaction of dicyclopentadienylcobalt complex **32** with organic halides.[91-93] In the proposed mechanism, the cobaltocene functions as an one electron donor in the first step, and as a radical trap in the second step (**Scheme 36**).

Scheme 36



32



32

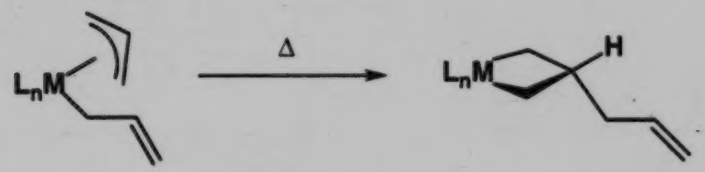
R = CCl_3, $C_6H_5CH_2$, CH_2I, $CHBr_2$

X = Cl, Br, I

Radical addition pathways have also been defined for reactions of radicals with the free olefin moiety of α,β–unsaturated carbene, η^2–alkenyne, η^1–allyl, and η^1–cyclopentadienyl ligands. Most common, however, are various ligand-to-ligand dimerization reactions observed for a range of odd-electron metal complexes.[97]

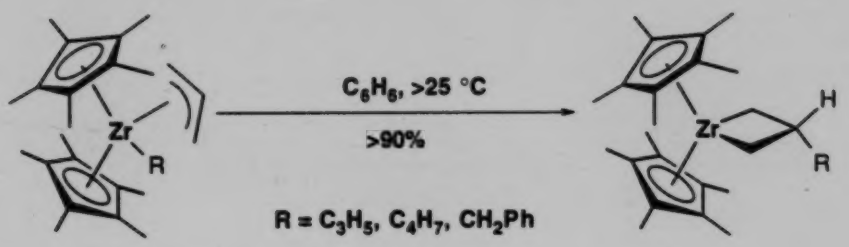
Tjaden and Stryker found that permethyl zirconocene bis(allyl) complex and similar systems undergo a thermal ligand rearrangement to yield the β-substituted

zirconacyclobutane complexes (**eq. 15**).[94] This process involves the migration of one of the allyl ligands to the β-carbon of another allyl ligand.



eq. 15

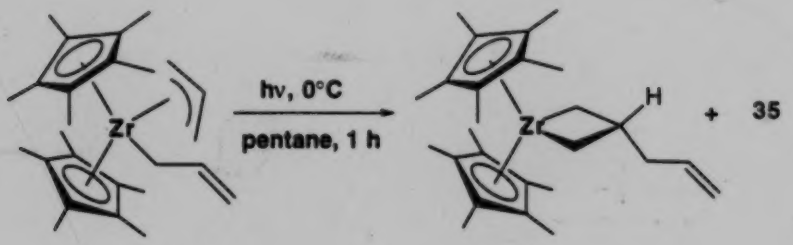
When [Cp*$_2$Zr(allyl)R] (R = allyl, benzyl, crotyl) is warmed to 50°C, the starting material is slowly consumed and the corresponding β-substituted zirconacyclobutane complex is produced in high yield (**eq. 16**). Under the same conditions, the allyl methyl or allyl phenyl complexes do not undergo such rearrangement, nor does the well-known unsubstituted zirconocene bis(allyl) Cp$_2$Zr(η^3-allyl)(η^1-allyl).



eq. 16

These rearrangements also occur under photolytic conditions. Photolysis of bis(allyl) complexes **35** at 0°C for 1 h produces a 1 : 1 mixture of zirconacyclobutane **36** and the starting bis(allyl) complexes **35** (**eq. 17**).[94,95] However, this reaction does not go to completion upon further photolysis. A brief mechanistic study supported a free radical mechanism for these rearrangements, in which a stabilized radical is formed by homolysis

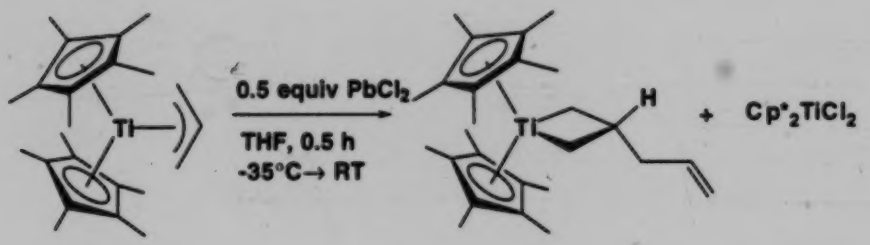
of a metal-carbon bond, followed by recombination to give a thermodynamically more stable product.



35 36

eq. 17

In another experiment, when complex $Cp^*_2Ti(\eta^3\text{-}C_3H_5)$ **37** is treated with $PbCl_2$, bis(allyl) complex **38** and $Cp^*_2TiCl_2$ **39** are obtained (**eq. 18**).[94,95] Although the reaction



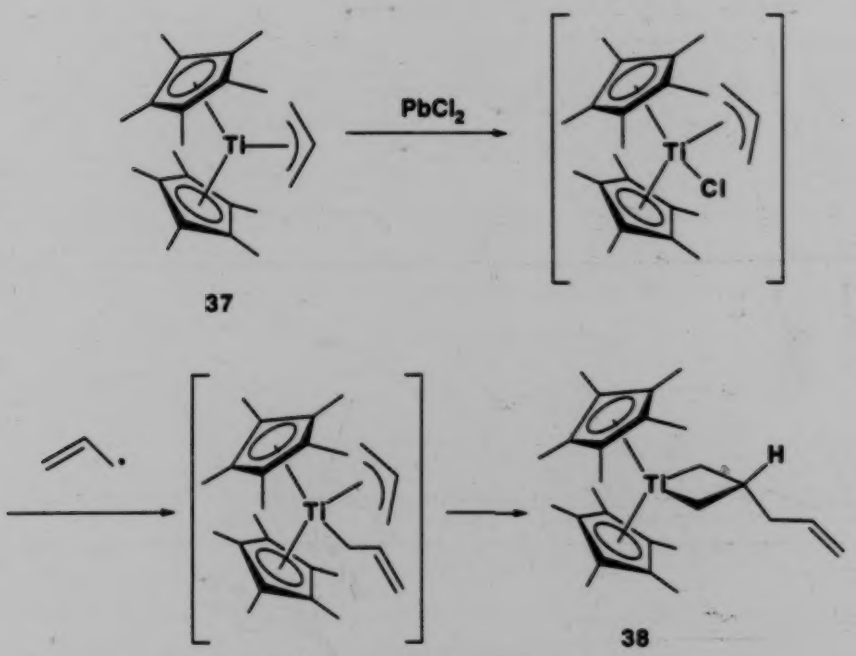
37 38 39

eq. 18

mechanism is not fully understood, most proposals invoke a radical coupling process involving the addition of an allyl radical and a Ti(III) allyl complex. One proposed mechanism assumes that oxidation of allyl complex **37** is slow, producing an unstable Ti(IV) allyl (chloride) intermediate which decomposes to form Cp^*_2TiCl and allyl radical. The former reacts with remaining $PbCl_2$ to afford $Cp^*_2TiCl_2$, while the latter reacts with

the remaining starting material to produce the allyl metallacyclobutane complex **38**, either by direct radical addition to central carbon of the η^3-allyl or by the formation of a transient bis(allyl) complex followed by allyl extrusion and rearrangement (**Scheme 37**).

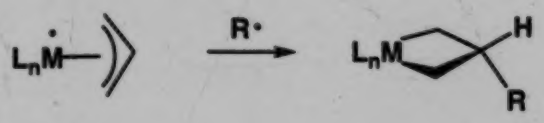
Scheme 37



Treatment of allyl complex **37** with allyl bromide similarly gives complex **38** and $Cp^*_2TiBr_2$. In this reaction, however, the yield of titanacyclobutane reproducibly exceeds 50 %, demanding that at least some of the metallacycle is formed by direct addition of allyl radical to complex **37**.

Based on these studies, various free radical addition reactions were investigated. The first central carbon alkylations of neutral d^1 titanocene π-allyl complexes with organic free radicals were reported by Casty and Stryker.[96,97] In this study, a general,

highly regioselective addition of organic radicals to an odd–electron η^3–allyl complex was reported (**eq. 19**).

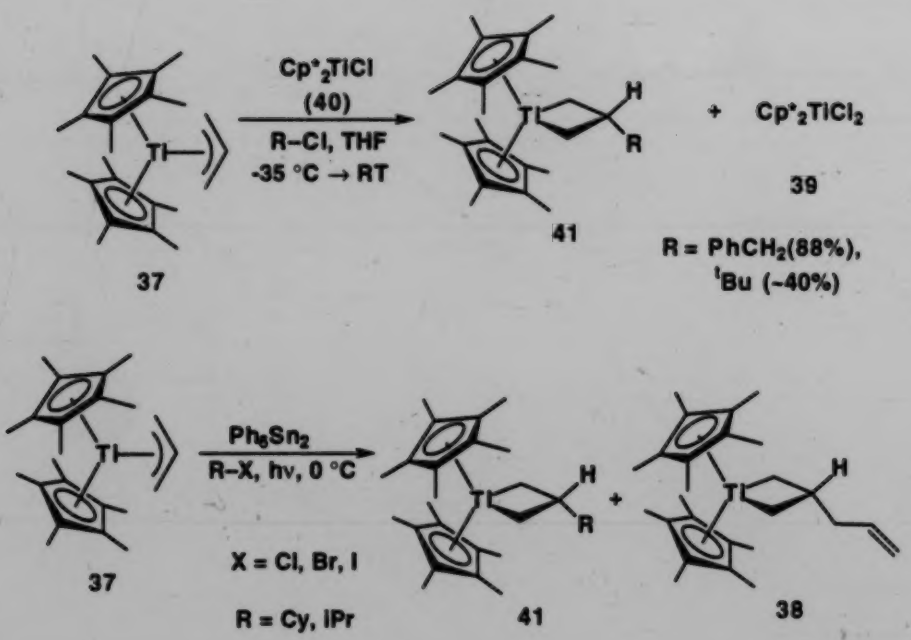


eq. 19

For example, when $Cp^*_2Ti(\eta^3\text{-}C_3H_5)$ **37** was treated with Cp^*_2TiCl **40** and an alkyl halide, the reaction gave central carbon alkylation, producing β-alkyl titanacyclobutane complexes **41** (**Scheme 38**). This radical generating strategy, however, is limited to activated organic halides; the tertiary organic chloride gave only a low yield of the titanacyclobutane complex. This restriction was attributed to the difficulty associated with generating non-activated radicals using complex **40**.

To extend this reaction, tin-based methodology was investigated. Standard tin hydride reagents require the use of radical initiators to generate the organic free radical, but the most popular initiator, AIBN, is incompatible with the early metal complexes. An alternative method using hexaphenyldistannane and an alkyl halide under photolytic conditions was used instead. This method enables the successful alkylation of allyl complex **37** with secondary organic radicals. With cyclohexyl iodide as the radical precursor, a mixture of β-cyclohexyl- and β-allyl-titanacyclobutane complexes, **41** and **38** are observed. Better selectivity is obtained using the corresponding cyclohexyl bromide, but the corresponding alkyl chloride gave the best results. The tin method thus extends the radical alkylation process to make titanacyclobutanes from secondary radicals and provides further evidence for a radical mechanism. The formation of the β-allyl titanacyclobutane complex **38** most probably results from the decomposition of the unstable titanium allyl iodide intermediate formed from direct oxidation of allyl complex by cyclohexyl iodide.

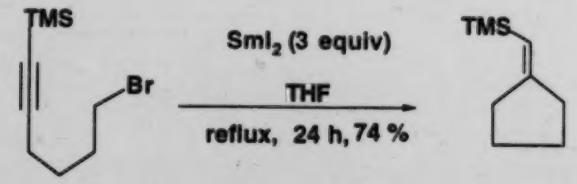
Scheme 38



Another investigation was based on the fact that the decomposition of (bis)alkyl mercury compounds produce the corresponding organic free radicals.[98] This method was investigated to see whether such a radical could be used for addition to allyl complex **37** and to provide further evidence for the radical process. The experiment results showed strong evidence for direct radical addition mechanism, but this method has practical limitations: low yield, difficult product separation, and only highly stabilized radicals can be used.

Samarium diiodide is a very popular reagent in organic synthesis; it is often used as one-electron reducing reagent and the reagent possesses excellent chemoselectivity in the reduction of carbonyl, alkyl halide, and α-heterosubstituted carbonyl substrates.[99-102] The reagent is also effective for the initiation of various free radical additions to alkenes

and alkynes. For example, alkynyl halides, when treated with samarium diiodide, convert to cyclized product in good yield (**eq. 20**).[103]



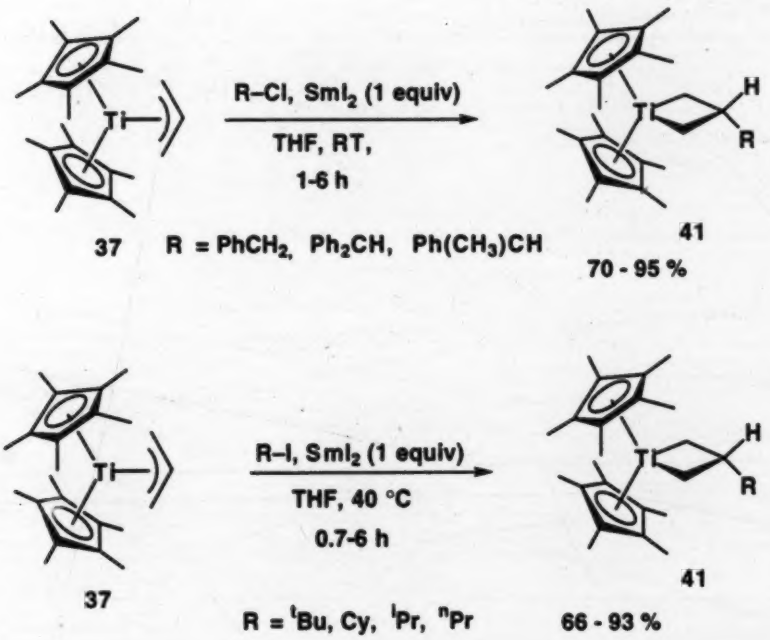
eq. 20

This reagent is commercially available in 0.1 M THF solution. Casty and Stryker tested its application in titanacyclobutane synthesis and the results showed that the samarium diiodide provides an efficient and convenient method for the preparation of a variety of β-substituted titanacyclobutane complexes. Both stabilized and unstabilized radicals can be added to the allyl complexes to form titanacyclobutane complexes and the products are easily separated and purified.[97]

Using this method, many different organic free radicals were generated and added to the central carbon of the η^3-allyl ligand in complex **37**, generating titanacyclobutane complexes in good to excellent yields (**Scheme 39**). For the benzylic cases, the use of low temperature and the less reactive chloride is necessary to inhibit both SmI_2-induced organic radical dimerization[104,105] and competitive reaction of the organic halide with the titanocene allyl complex. For simple alkyl halides, the use of the iodide and higher temperature is required to provide central carbon alkylation products efficiently (**Scheme 39**). In all the cases, the crude reaction mixture was triturated with pentane after evaporation of the solvent, separating the Sm(III) byproducts from the product solution, providing a very convenient method for work–up.

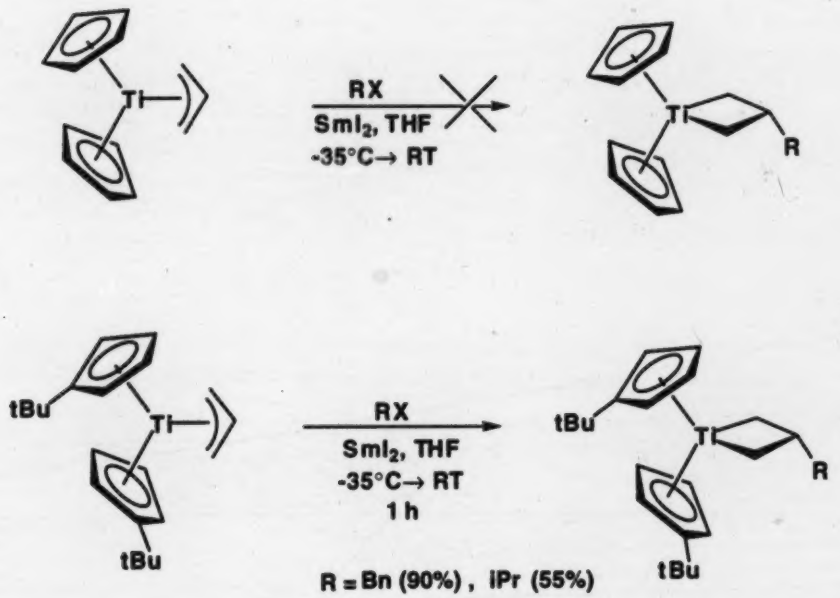
In order to investigate electronic and steric effects on the radical alkylation, the simple unsubstituted cyclopentadienyl ligand was investigated. This ligand set provides a less electron rich metal center relative to the pentamethylcyclopentadienyl ligand set.

Scheme 39



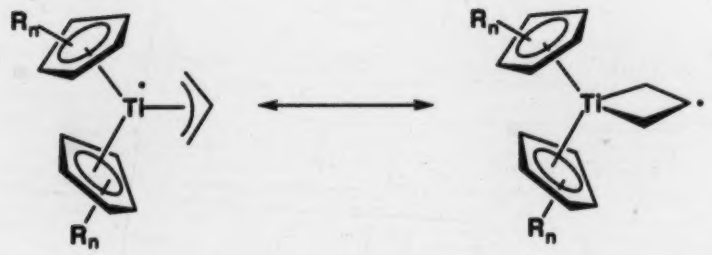
Using optimized reaction conditions from the C_5Me_5 ligand set, central carbon alkylation is not observed when $Cp_2Ti(\eta^3\text{-}C_3H_5)$ is treated with SmI_2 and an alkyl halide. Primarily, decomposition products are obtained.[91,96] The slightly more electron rich complex $(t\text{-BuCp})_2Ti(\eta^3\text{-}C_3H_5)$, under same reaction conditions, successfully undergoes alkylation (**Scheme 40**). In addition, the *t*-BuCp and C_5Me_5 titanacyclobutanes prepared by this method are considerably more stable toward [2+2] cycloreversion than are those prepared using the unsubstituted cyclopentadienyl ligand (*vide infra*)

Scheme 40



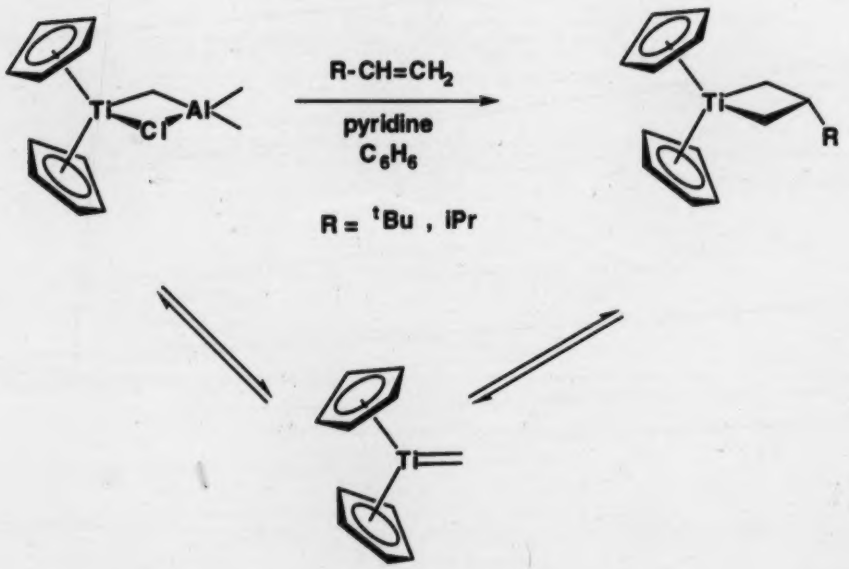
These observations suggest that high electron density at titanium is a requirement for successful central carbon alkylation. Perhaps a high electron density at the metal center destabilizes the singly occupied metal orbital, increasing metal d→π* allyl back-bonding into the π*-orbital of the allyl ligand. The enhanced back-bonding also increases the preference for η^3-coordination of the allyl. In valence bond terms, this means that there is a greater delocalization of the odd-electron density onto the central carbon of the allyl ligand. This imparts more radical character onto the central carbon and facilitates radical alkylation and enhanced central carbon regioselectivity, as illustrated by the resonance structure shown in **Scheme 41**. [106] The electron rich ligands also stabilize the higher oxidation state Ti(IV) products and may provide a greater thermodynamic driving force for the alkylation.

Scheme 41



The 'classical' method for the preparation of titanacyclobutane complexes uses the Tebbe reagent and a substituted olefin; the titanacyclobutane products are generated by a [2+2] cycloaddition process (**Scheme 42**).[107-110] When the reaction is performed in

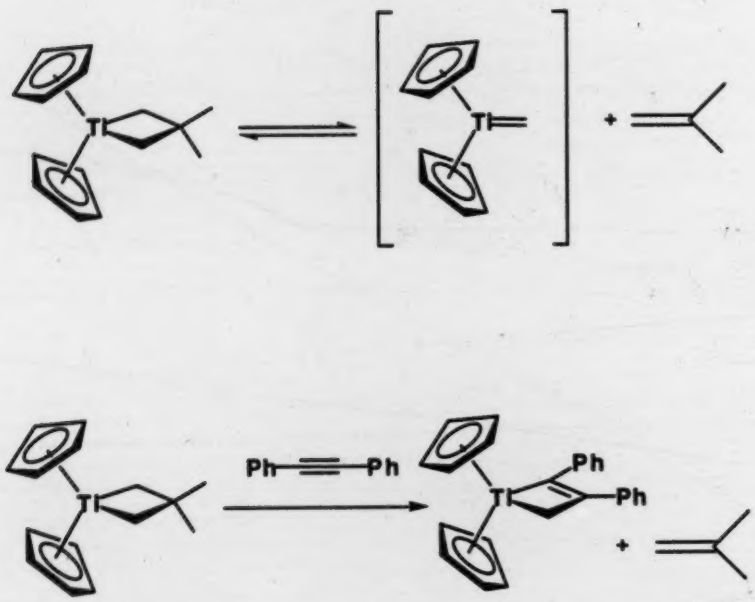
Scheme 42



THF, however, no titanacyclobutane product is obtained. When the reaction is performed in benzene containing 1 equiv of pyridine, the titanacyclobutane product and a pyridine-dimethylchloroaluminum adduct are produced in quantitative yield. Separation of the products is difficult.

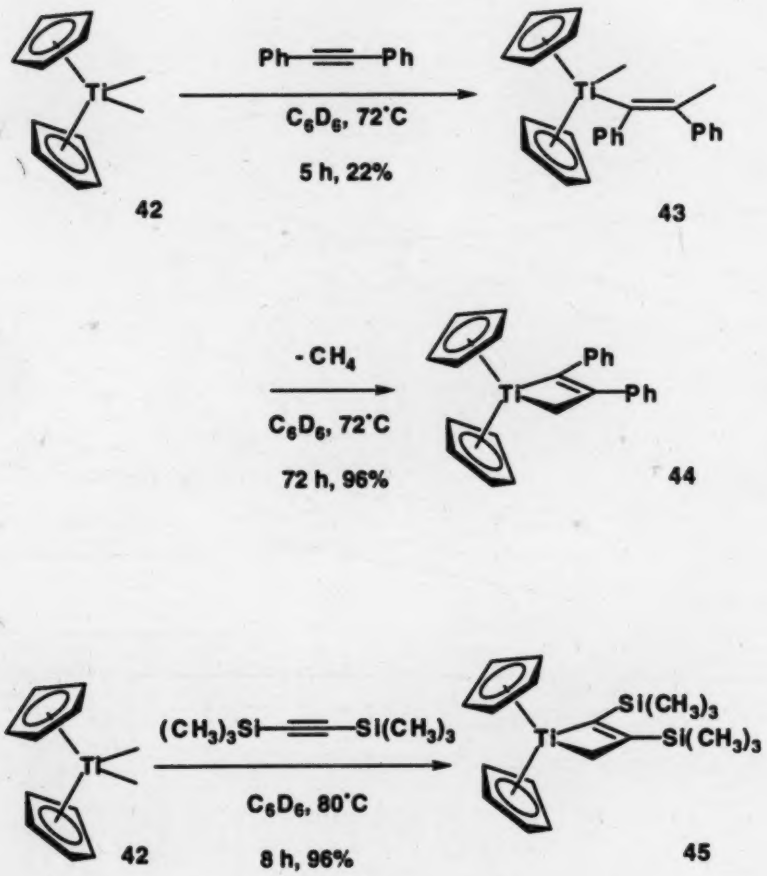
Further investigation found that the titanacyclobutane complexes are thermally unstable, resulting in a retro [2+2] cycloadditon to give an olefin and a titanium methylidene intermediate (**Scheme 43**). The intermediate can be trapped with diphenylacetylene to afford the more stable titanacyclobutene complex.

Scheme 43



Later investigation by Doxsee[111] found that the reaction of dimethyltitanocene with diphenylacetylene produces a vinyl complex resulting from insertion of the alkyne into one of the titanium-methyl bonds. Thermolysis of the vinyl complex results in the formation of the titanacyclobutene complex and at the same time methane formation is detected (**Scheme 44**). The reaction of dimethyltitanocene with bis(trimethylsilyl)acetylene in dry benzene (80°C, 10 h) yields the known compound[112] bis(trimethylsilyl)titanacyclobutene **45** in quantitative yield. Interestingly, in this reaction, no intermediates are observed during the course of the reaction. When dimethyltitanocene is treated with diphenylacetylene at 35°C, the simple insertion product **43** is obtained in nearly quantitative yield, along with a trace amount of diphenyltitanacyclobutene **44** (Complex **43** was previously reported as a minor product by Rausch[113,114]during a photochemistry investigation.). Continued thermolysis at higher temperature (70°C) completes the conversion of the vinyl complex **43** to the corresponding titanacyclobutene complex **44** and methane. When another alkyne was added during the thermolysis of complex **43**, only **44** was observed; no new titanacyclobutenes were detected. This control experiment rules out the reversion reaction of complex **43** to dimethyltitanocene via loss of alkyne under the reaction conditions. Several other alkynes were treated with the dimethyltitanocene at elevated temperature, giving corresponding substituted titanacyclobutene complexes. Although this investigation provides a convenient method for the preparation of some titanacyclobutene complexes, it has limitations, as only a limited number of symmetrical alkynes work well and terminal alkynes do not undergo such a reaction. For example, when dimethyltitanocene is treated with 3-hexyne, a competitive alkyne polymerization reaction occurs. The same problem occurs when 2-butyne is treated with the dimethyltitanocene, gaving irreproducible and variable yields of the dimethyltitanacyclobutene products. For unsymmetrical alkynes, the reaction gives a mixture of two regioisomeric metallacyclobutene products. For example, when (trimethylsilyl)propyne is treated with dimethyltitanocene, it gives a 43 : 57 mixture of the

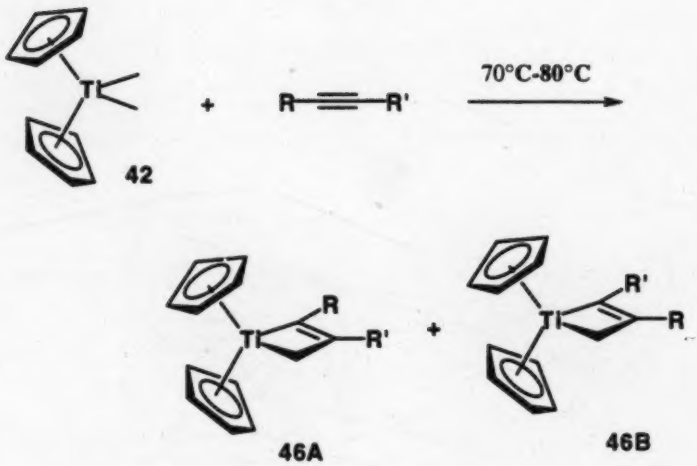
Scheme 44



two isomers (**Scheme 45**). The use of Tebbe's reagent instead of complex **42** gives similar mixtures of regioisomers.[115] These results suggest that the two reactions may involve the same intermediate.

These unfavorable factors limit the application of this method. For developing practical applications of titanacyclobutanes and titanacyclobutenes in organic synthesis, new synthetic methods need to be developed.

Scheme 45



R	R'	yield (%)
Me_3Si	Me_3Si	>95
Ph	Ph	>95
Et	Et	70 + polymer
Me	Me_3Si	43 % 57 %

2. *Free Radical Alkylation of Transition Metal Propargyl Complexes*

Transition metal allyl complexes have many important applications in organic synthesis.[107,108,110,116-118] The structurally related transition metal propargyl complexes are not yet so popular. Recently, however, metal propargyl complexes have received more and more attention. Metal propargyl complexes show some similarities to metal allyl complexes, but possess their own unique properties due to the presence of a

carbon-carbon triple bond instead of a double bond. For example, η^1-propargyl complexes can undergo a 1,3-shift to form the structurally distinct η^1-allenyl isomers (**eq. 21**).

eq. 21

Transition metal η^1-allyl and η^1-propargyl complexes show similar reactivity toward electrophiles.[119-121] For example, both complexes can undergo proton addition at the γ-carbon, forming cationic alkene and allene complexes.

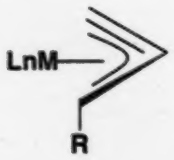
In the η^3-propargyl complexes **47**, a π–bonded propargyl radical acts as a three electron donor, which is similar to the π–bonded allyl radical. The coordinated propargyl ligand is different from free alkyne; it is bent instead of straight. The main structural difference between allyl complex and propargyl complex is that the propargyl ligand carbons and the metal are coplanar while the allyl ligand is side–on bonded through its π–system (**Scheme 46**).

Prior to the synthesis of propargyl complexes **47**, Pd propargyl complexes were proposed as intermediates in some Pd catalyzed reactions[122] and structurally related η^3-butenynyl complexes **48** were successfully made. These compounds include osmium, ruthenium, tungsten, and iron complexes.[123-126]

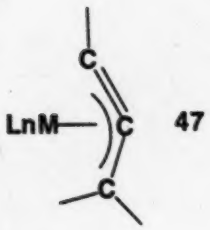
The first isolated unsubstituted η^3-propargyl complex was made by Krivykh,[127] by photolysis of $C_6Me_6Mo(CO)_3$ and propargyl alcohol in the presence of HBF_4 (**eq. 22**).

Scheme 46

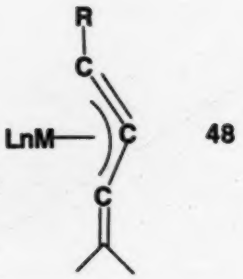
allyl complex



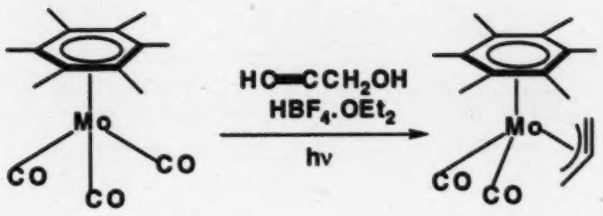
Propargyl complex



47



48

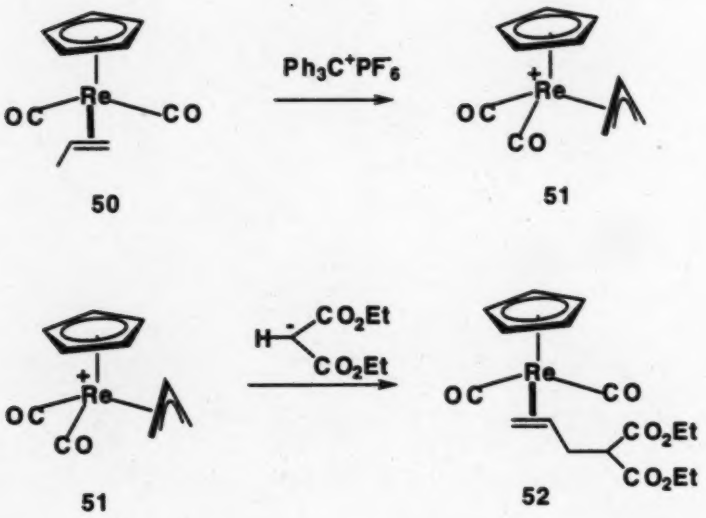


49

eq. 22

In 1990, Casey reported the synthesis of the cationic η^3-allyl rhenium complex $C_5H_5(CO)_2Re(\eta^3\text{-}CH_2CHCH_2)^+PF^-_6$ **51** by hydride abstraction from the rhenium-propene complex $C_5H_5(CO)_2Re(CH_2{=}CHCH_3)$ **50**. Further reaction of this complex with carbon nucleophile results in a terminal carbon addition product **52** (**Scheme 47**).[128]

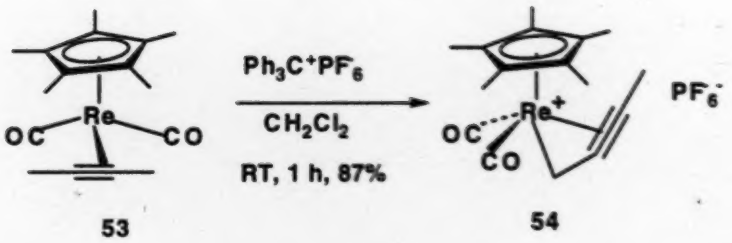
Scheme 47



The experience in hydride abstraction from rhenium-alkene complexes directed them to investigate the same reaction on rhenium-alkyne complexes. When $Cp^*Re(CO)_2THF$[129] was treated with excess 2-butyne, $Cp^*Re(CO)_2CH_3C{\equiv}CCH_3$ **53** was obtained. Hydride abstraction from rhenium alkyne complex **53** gave the η^3-propargyl complexes **54** in high yield (**Scheme 48**).

The structure and bonding of η^3-propargyl complexes are often discussed by invoking the η^3-allenyl resonance structure. The large $^1J_{C\text{-}H}$ = 170 Hz coupling of the propargyl CH_2 group represents the importance of the η^3-allenyl resonance structure **55** (**Scheme 48**).[130]

Scheme 48

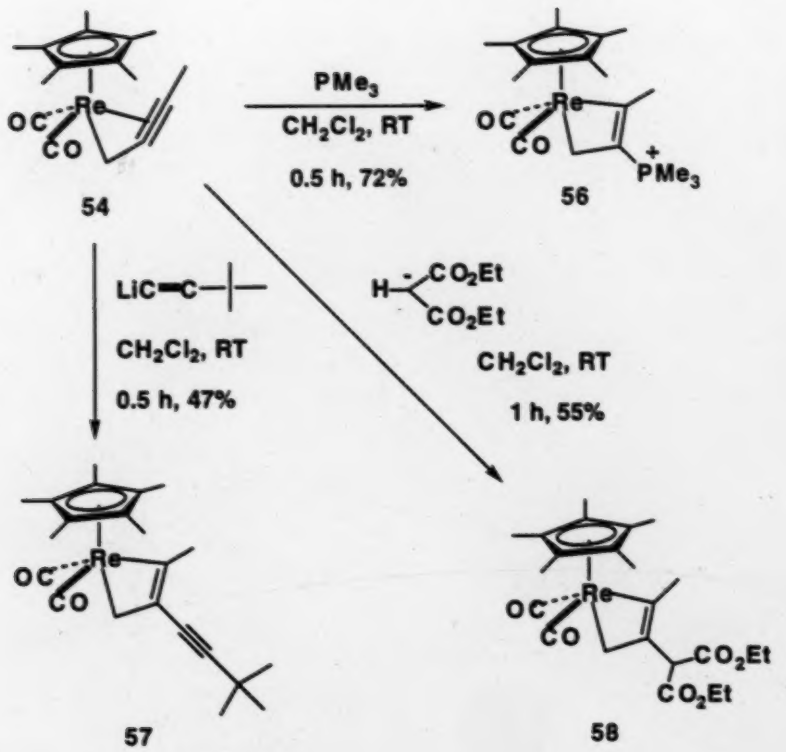


53 54

55

The η^3-propargyl complexes **54** reacts with a variety of nucleophiles to afford the corresponding rhenacyclobutene complexes.[130] The nucleophile adds exclusively to the central carbon of the η^3-propargyl ligand. For example, treatment of the η^3-propargyl complexes **54** with PMe_3 in dichloromethane afforded a phosphine substituted rhenacyclobutene complex **56**. When $LiC{\equiv}CCMe_3$ and $NaCH(CO_2Et)_2$ are used as a nucleophile, neutral rhenacyclobetene complex **57** and **58** are obtained (**Scheme 49**). Casey speculated that nucleophilic attack at central carbon may relieve some strain in the starting η^3-propargyl complexes.

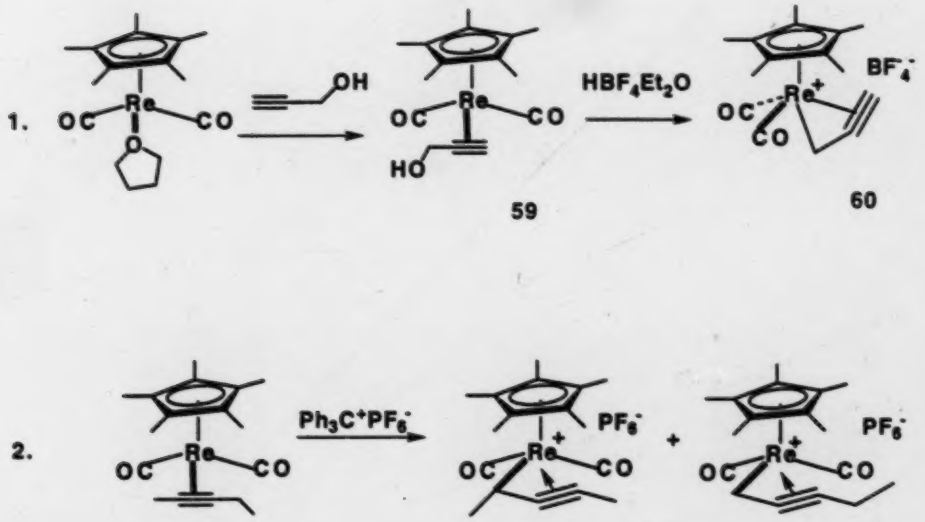
Scheme 49



Another method to prepare the η^3-propargyl rhenium complexes is by protonation of η^2-propargyl alcohol complexes, prepared by the reaction of $C_5Me_5(CO)_2Re(THF)$ with propargyl alcohol.[131] Treatment of complex **59** with HBF_4 in dichloromethane at low temperature led to the clean generation of the complex **60** which was characterized at low temperature by ^1H NMR, ^{13}C NMR and IR spectroscopy (**Scheme 50, entry 1**). The unsubstituted η^3-propargyl rhenium complexes **60** can be isolated at 0°C and handled at room temperature for a short time (less than one hour). The protonation of rhenium propargyl alcohol complexes provides a more versatile route to η^3-propargyl complexes because of its regiospecificity and tolerance of terminal alkynes. The hydride abstraction

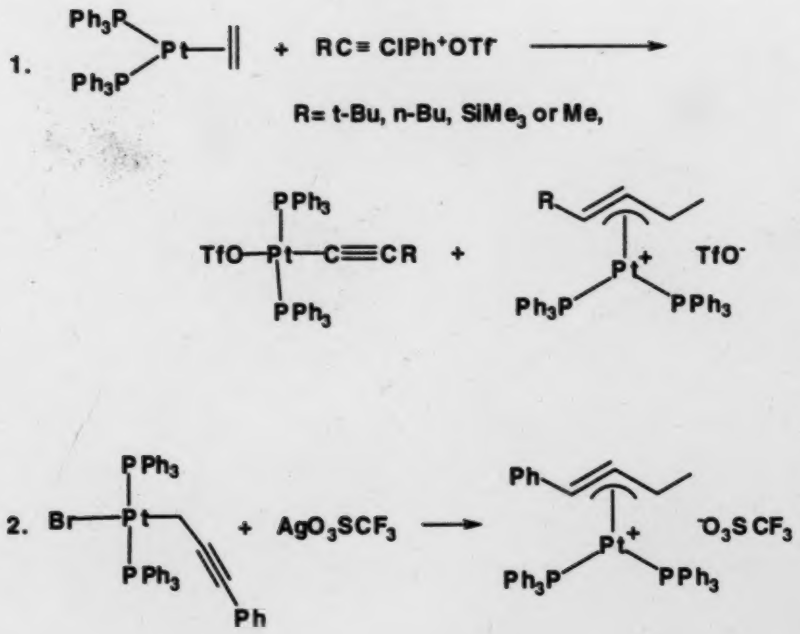
method is clean and the starting material is easy to make, but the reaction gives low regioslectivity (**Scheme 50, entry 2**) and fails for terminal alkynes.

Scheme 50



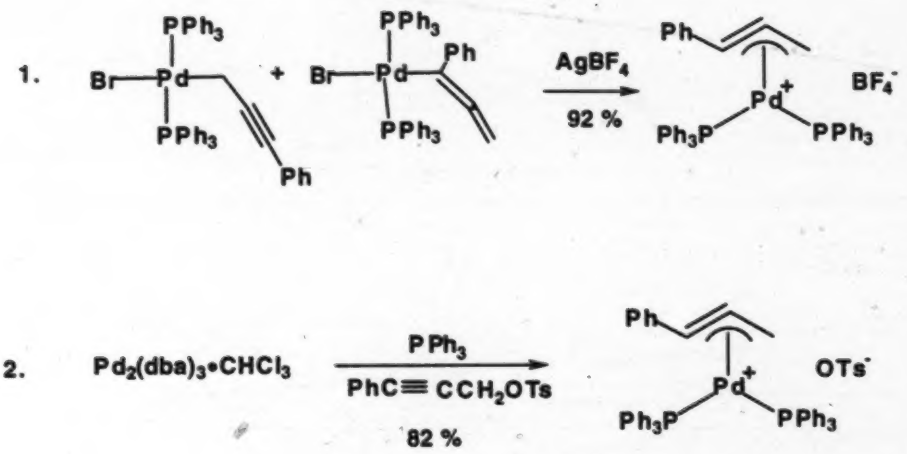
There are several different ways to make platinum η^3-propargyl complexes. Stang[132] uses $(PPh_3)_2Pt(\eta^2\text{-}C_2H_4)$ to react with $[RCCIPh]O_3SF_3$ (R= t-Bu, n-Bu, $SiMe_3$ or Me); the reaction yields the Pt η^3-propargyl complex along with a Pt alkynyl complex as a coproduct (**Scheme 51, entry 1**). Chen[133] and Wojcicki[134] reported the synthesis of Pt η^3-propargyl complexes using *trans* $(PPh_3)_2BrPt(\eta^1\text{-}CH_2C{\equiv}CPh)$ and analogous (**Scheme 51, entry 2**). The starting η^1–propargyl complexes were prepared by oxidative addition of the propargyl halide to Pt(0)

Scheme 51

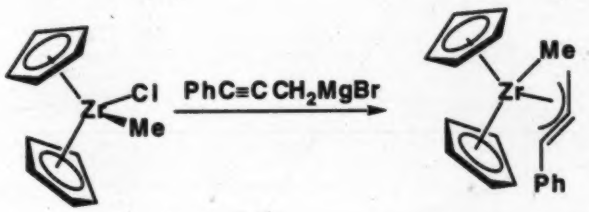


Treatment of the isomeric mixture of *trans* $(PPh_3)_2BrPd\eta^1$-$CH_2C{\equiv}CPh$) and *trans* $(PPh_3)_2BrPd(\eta^1$-$CR{=}C{=}CH_2$ (R = Ph, Me), prepared by the general method of Boersma,[135] with $AgBF_4$ in dichloromethane solution produces the Pd η^3-propargyl complexes in 90 %-92 % yield (**Scheme 52, entry 1**). This Pd η^3-propargyl product can also be prepared by oxidative addition of $RC{\equiv}CCH_2OSO_2C_6H_4Me$-p to $Pd_2(dba)_3{\cdot}CHCl_3$ and PPh_3 in dichloromethane, followed by stirring at room temperature. This method affords the Pd η^3-propargyl complexes product in 82 % yield (**Scheme 52, entry 2**).[136] The latter method gives a tosylate salt which is stable to isolation. In contrast, the use of $RC{\equiv}CCH_2OSO_2C_6H_4Me$-p and $(PPh_3)_2Pt(\eta^2$-$C_2H_4)$ gives corresponding Pt η^3-propargyl complexes that decompose during work–up.

Scheme 52



One zirconium η^3-propargyl complex has been made, by the reaction of $Cp_2Zr(CH_3)Cl$[137] with $PhC{\equiv}CCH_2MgBr$[138] (**eq. 23**).

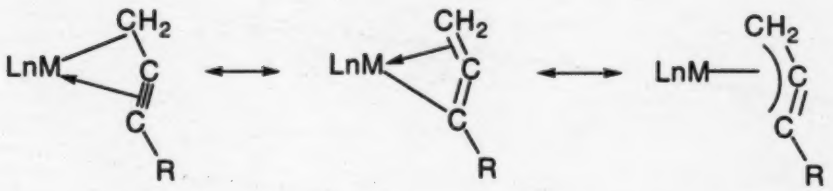


eq. 23

Single-crystal X-ray analysis of different η^3-propargyl complexes show that the η^3-C_3 skeleton is bent, with the propargyl C-C-C angle around 150°, which is greater than the angle of η^3-allyl complexes (120°).[116,139] In most complexes, the metal atom is nearly coplanar with the propargyl ligand. The two carbon-carbon bond distances in the propargyl ligand are different; the C-CH_2 bond length is 1.34-1.40 Å, longer than the C=C double bond in free allenes, and the common carbon-carbon double bond, but shorter than

the common carbon-carbon single bond. The C≡CR bond length is 1.23-1.29 Å, this length is between that of a common carbon-carbon triple bond and a carbon-carbon double bond length. Usually, the following resonance structures are used to describe the η^3-propargyl complexes in valence bond terms (**Scheme 53**).

Scheme 53

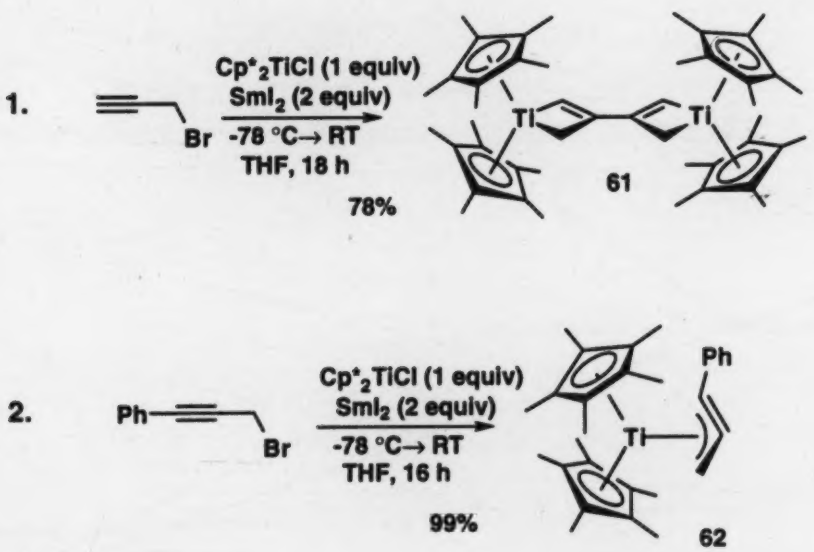


The distance from the metal to the methylene carbon of the propargyl ligand is shorter than the distance from metal to the CR terminal carbon, but similar to the distance from metal to the central carbon of the propargyl ligand. The η^3-propargyl ligand also contains a C=C π bond which is not involved in interaction with the metal. This orthogonal π bond is unique.

The discovery of transition metal propargyl reactions is often related to the chemistry of the corresponding allyl complexes. As discussed, Casey reported the synthesis of the cationic η^3-allyl rhenium complex $C_5H_5(CO)_2Re(\eta^3\text{-}CH_2CHCH_2)^+PF^-_6$ by hydride abstraction from the rhenium-propene complex $C_5H_5(CO)_2Re(CH_2{=}CHCH_3)$, which led them to investigate the same reaction on the rhenium alkyne complex, resulting in the synthesis of rhenium η^3-propargyl complexes. Similarly, the success of free radical addition to Ti(III) η^3-allyl complexes in the Stryker group led to an investigation of same reaction using the previously unknown Ti(III) η^3-propargyl complexes. Ogoshi first attempted the synthesis of titanium propargyl complexes by the reaction of Cp^*_2TiCl with allenyllithium, the same method used for the

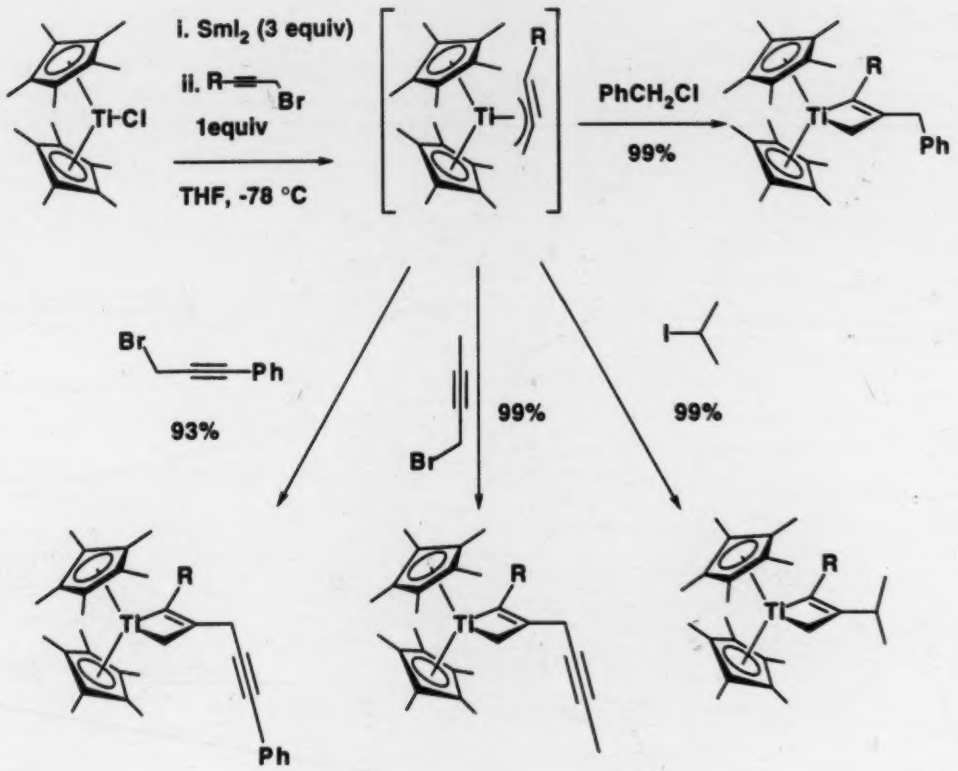
synthesis of the titanium alkyl and allyl complexes.[140] This method failed to produce the propargyl complex but gave a low yield of the β–carbon to β–carbon dimerization product **61** (**Scheme 54**). Later, a better method was developed for the preparation of dimeric complex **61**. Thus, treatment of Cp^*_2TiCl with propargyl bromide in the presence of two equivalents of SmI_2 gives complex **61** in 78 % isolated yield (**Scheme 54, entry 1**). Under same conditions, the reaction of Cp^*_2TiCl with 1-phenyl-3-bromopropyne indeed gives the titanium (III) η^3-phenylpropargyl complex **62** in quantitative yield.[141] (**Scheme 54, entry 2**) No dimerization of complex **62** is observed.

Scheme 54



Further investigation found that titanium(III) η^3-propargyl complexes, even those that dimerize in solution, can also undergo the free radical addition reactions, giving titanacyclobutene complexes (**Scheme 55**).[141] The addition reaction occurs exclusively

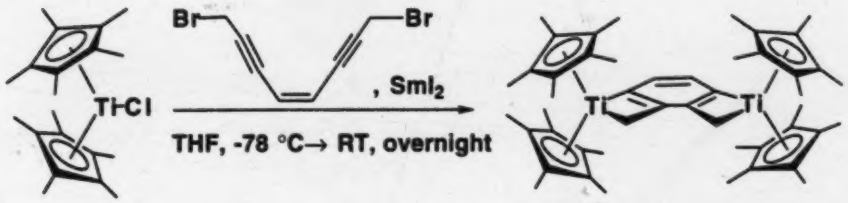
Scheme 55



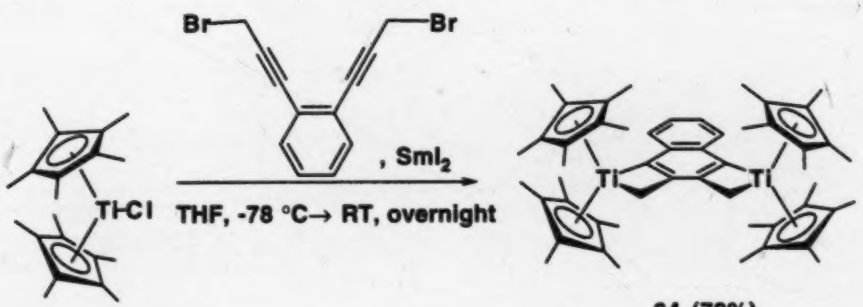
at the central carbon of the propargyl ligand and provides a convenient and highly regioselective synthetic method for the preparation of disubstituted titanacyclobutene complexes. Thus, a reaction mixture containing Cp^*_2TiCl, three equivalents of SmI_2, 1 equivalent propargyl halide, and one equivalent of an alkyl halide results in the formation of the 2,3-disubstituted titanacyclobutene complex in high yield (**Scheme 55**). The reaction almost certainly proceeds via a titanium η^3-propargyl intermediate, although only the phenylpropargyl complex **62** can be isolated. The generality and controlled

regioselectivity of this metallacyclobutene synthesis contrasts with titanacyclobutene synthesis via titanium alkylidene/alkyne [2 + 2] cycloaddition, the only other methodology available for preparation of titanacyclobutene complexes.

Scheme 56



63 (83%)



64 (72%)

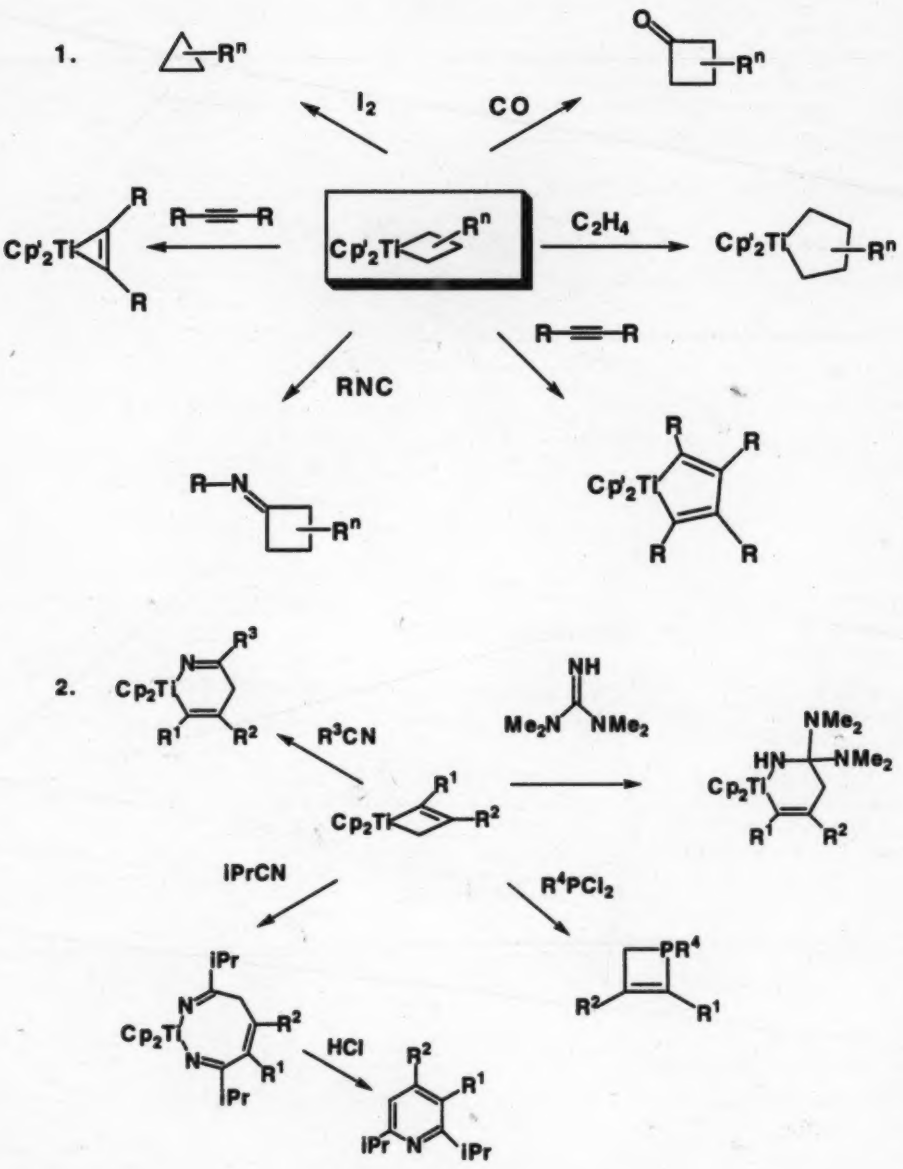
With specially designed bis(propargyl halide) substrates, an intramolecular version of the dimerization reaction yields the dititanacyclobutene complexes **63** and **64** (**Scheme 56**). It is not yet known whether the aromaticity of the product is essential to this intramolecular pseudodimerization.

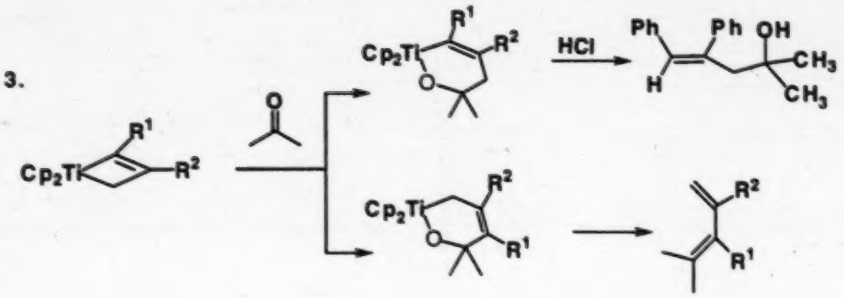
B. Project Goals

Titanacyclobutane and titanacyclobutene complexes are important complexes in organometallic chemistry. These complexes undergo many interesting transformations to produce various important organic and organometallic compounds as showed in the following scheme (**Scheme 57, entries1-3**).[139a-c] The addition of organic radicals to titanium(III) allyl and propargyl complexes provides a highly regioselective method for the preparation of titanacyclobutane and titanacyclobutene complexes. This is a new carbon–carbon bond forming reaction with the potential for applications in synthetic organic chemistry. We propose to develop and improve this methodology to be more general and synthetically useful. First, we plan to concentrate on intramolecular free radical cyclizations of titanium(III) propargyl complexes, to investigate the scope of the reaction. Nomura and Stryker previously investigated intramolecular cyclization reactions of titanium(III) allyl complexes using Cp^*_2TiCl and α,ω–bis(allylbromide) substrates. When the nine-carbon bis(allyl bromide) substrate **65a** was treated with Cp^*_2TiCl in the presence of SmI_2, a 6-member ring titanacyclobutane complex **66a** was obtained in high yield with the formation of an undetermined single stereoisomer (**Scheme 57, entry 4**). When the reaction was applied to a 7-member ring anologue synthesis, only a trace amount of the product was obtained (**Scheme 57, entry 5**). Attempts to make the 8-member ring analogue was not successful (**Scheme 57, entry 6**).[142]

Interestingly, in the titanium propargyl chemistry, Ogoshi and Stryker also tried one similar intramolecular cyclization reaction, using Cp^*_2TiCl and an α,ω–propargyl dihalide substrate. A six-member ring titanacyclobutene complex **68** was isolated in high yield (**eq. 24**).[141]

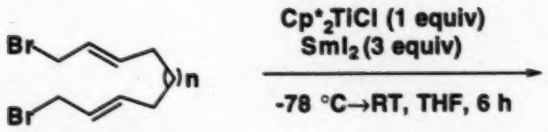
Scheme 57



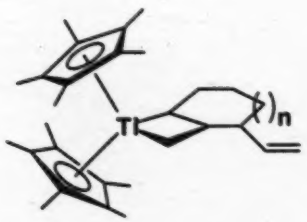


The experience in titanium allyl chemistry and our desire to develop this reaction into general methodology directed us to investigate the possibility of synthesizing bicyclic complexs with other ring sizes, especially those with seven- to ten-membered rings. If such reactions are successful, the cyclization can then be developed into a

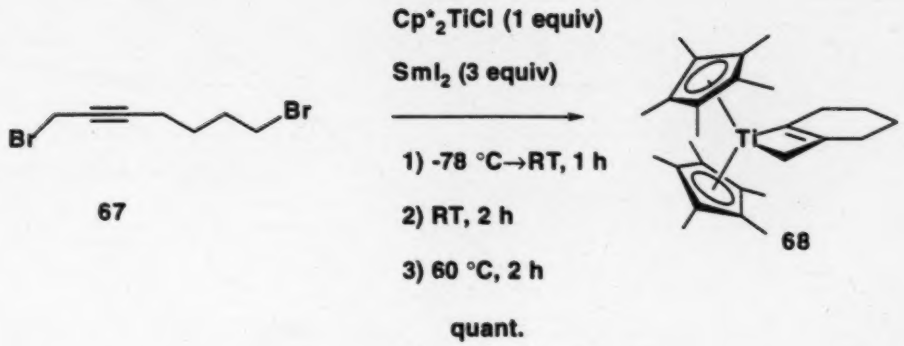
Scheme 57



4	65a, n = 1
5	65b, n = 2
6	65c, n = 3



66a, (n = 1, 90%)
66b, (n = 2, trace)
66c, (n = 3, 0 %)



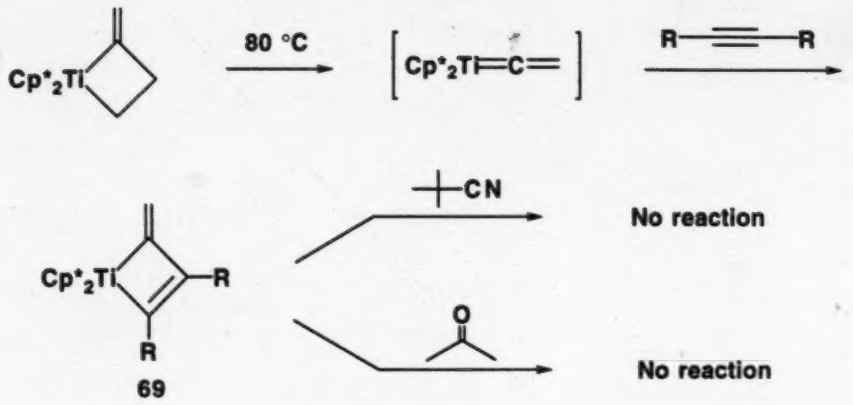
eq. 24

general method for the preparation of bicyclic compounds from an acyclic substrate, a synthetically interesting method. We further planned to develop some insertion reactions using the bicyclic products, including ketone insertions, isonitrile insertions and other titanum–directed carbon–carbon bond forming reactions. After such insertion reactions, demetallation is expected to give interesting mono- and bicyclic organic compounds.

A second major goal of this project is to investigate the steric and electronic features of different ancillary ligand sets that support the addition of organic free radicals to the η^3–propargyl ligand. The Cp* ligand system has several limitations and drawbacks to its use in this reaction. For example, the starting material, Cp^*_2TiCl, is difficult to make due to the expense of Cp*H; this limits it's potential in synthetic applications, especially in large scale synthesis.

Beckhaus[143] and co-workers made a different type of titanacyclobutene complex using the [2+2] reactivity pattern, in which both α-carbon atoms are sp^2 hybridized (**Scheme 58**). When α–methylenetitanacyclobutene complex **69** was treated with ketones and nitriles, however, no insertion reaction occurs[118,144,145] (**Scheme 58**). The lack of reactivity is attributed to the sterically hindered metal center, a result of the large Cp* ligands.

Scheme 58



69

We have also found that bis(Cp*) titanacyclobutene complexes are very stable, which diminishes the possibility of insertion and demetallation reactions. Our goal is to find better and more useful ligand systems for the Ti(III) propargyl chemistry. These ligand systems must be easy to make and use, and should be applicable not only to the intramolecular free radical reactions, but also to intermolecular free radical reactions. By investigating and comparing the reactivity and selectivity of different ligand systems, we can also gain a better understanding of how the electronic and steric features effect the alkylation reaction. Finally, the ligand system must accommodate insertion and demetallation reactions. In this way, a new synthetic method for the preparation of cyclic olefins will be developed. In addition, we planed to develop an improved method for the preparation of titanacyclobutane complexes and we hope that the titanacyclobutane complex can be made in one pot, without isolation of the allyl complex.

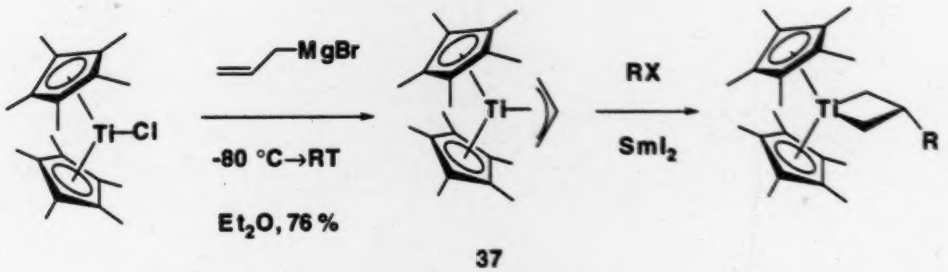
C. Results and Discussion

1. An Improved Method For The Synthesis of Titanacyclobutane Complexes

a. Introduction

The established method for the preparation of the titanacyclobutane complexes by radical alkylation involves two individual reactions. In the first reaction, Cp^*_2TiCl is treated with the allyl Grignard reagent to afford the $Cp^*_2Ti(\eta^3\text{-}C_3H_5)$ complex **37**. In the second reaction, $Cp^*_2Ti(\eta^3\text{-}C_3H_5)$ complex **37** undergoes free radical alkylation to generate the titanacyclobutane product (**Scheme 59**).

Scheme 59

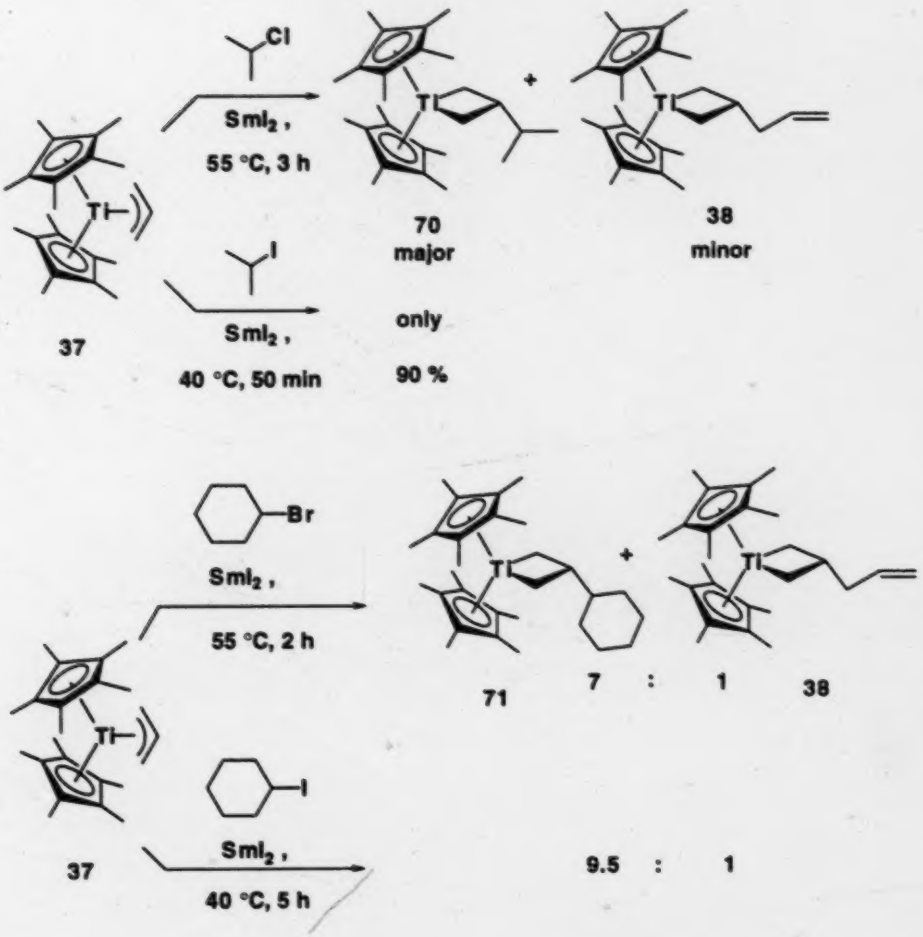


37

In this method, the first step reaction was reported by Luinstra.[140] Although the yield can be improved dramatically over the original report, it is still necessary to separate and purify the titanium(III) allyl complex intermediate. A second problem is that the alkylation reaction often gives two products. For example, when $Cp^*_2Ti(\eta^3\text{-}C_3H_5)$ is treated with isopropyl chloride in the presence of SmI_2, isopropyl titanacyclobutane complex **70** is produced along with a minor product, the allyl titanacyclobutane complex **38** (**Scheme 60**). When isopropyl iodide is used instead of the isopropyl chloride, complex **70** is formed exclusively. However, this improvement has limitations; when $Cp^*_2Ti(\eta^3\text{-}C_3H_5)$ is treated with cyclohexyl bromide in the presence of SmI_2, the

reaction also produces two products: cyclohexyl titanacyclobutane complex **71** and the allyl titanacyclobutane complex **38**. When cyclohexyl iodide is used under otherwise identical conditions, the reaction again gives two products. Although the ratio of the two products improves slightly, the by-product formation can not be avoided by using the corresponding iodide substrate (**Scheme 60**).[96]

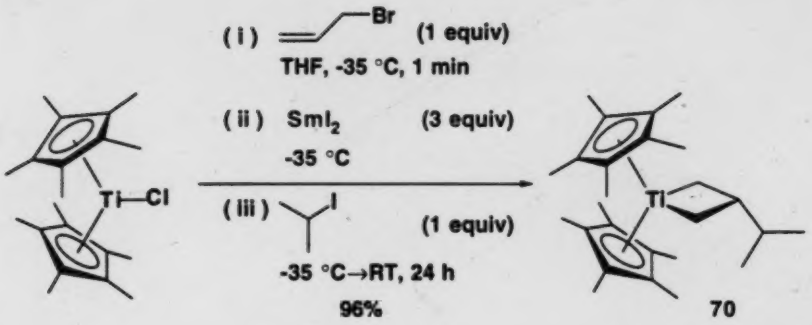
Scheme 60



Later, Greidanus found that with other ligand systems, it is not necessary to separate the titanium(III) allyl complex; the two step reaction sequence can be performed in one pot.[146] This improvement simplified the reaction operation; but the method still uses a Grignard reagent and is not desirable for synthetic applications, especially intramolecular reactions.

b. One pot synthesis of titanacyclobutane complexes using Cp^*_2TiCl

An improved one–pot titanacyclobutane forming method that avoids the use of allyl metal reagents has been realized. In the initial test, a solution of Cp^*_2TiCl in THF was mixed with a solution of SmI_2 in THF and cooled to low temperature. A solution of allyl bromide in THF was then added at low temperature (-78°C). After 10 minutes, a THF solution of isopropyl iodide was added at -78°C. The resulting reaction mixture was allowed to warm gradually to room temperature and then heated at 50°C for 3 h. No desired product was found in the reaction mixture. When the isopropyl iodide was replaced by benzyl chloride under similar conditions, the reaction still did not produce the desired titanacyclobutane complex. Using $[Cp_2TiCl]_2$ instead of Cp^*_2TiCl resulted only in the formation of decomposition products. Finally, the experimental procedure was substantially changed: a solution of allyl bromide in THF was mixed first with Cp^*_2TiCl at low temperature (-35°C). The reaction solution was shaken for about 1 minute and then a solution of SmI_2 in THF was added at -35°C. Finally, a solution of isopropyl iodide in THF was added to the reaction mixture, and the solution was allowed to warm to room temperature and maintained at room temperature for 22 h. After work–up, the desired titanacyclobutane complex, 1,1-bis(pentamethylcyclopentadienyl)-3-isopropyltitanacyclobutane **70** was obtained in quantitative yield (**eq. 25**). The complex **70** was spectroscopically homogeneous and identical to an authentic sample .[97]

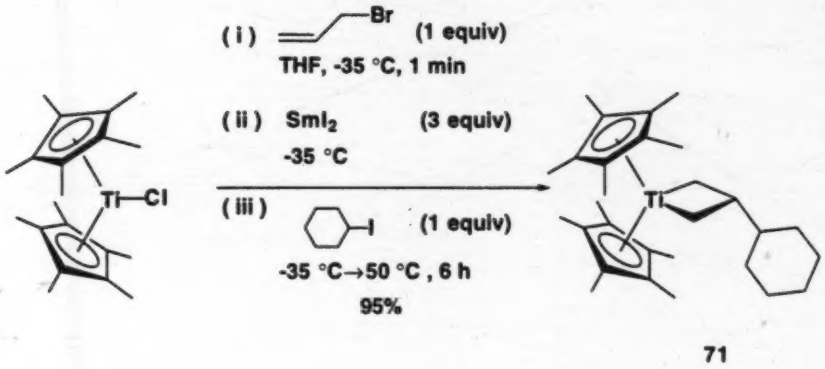


eq. 25

In another case, the cyclohexyl titanacyclobutane complex **71** was also obtained in high yield using the similar procedure: a solution of allyl bromide in THF was mixed with Cp^*_2TiCl at -35°C. After the resultant solution was shaken for about 1 minute, a cold solution of SmI_2 in THF was added at -35°C. The reaction mixture was then treated with cyclohexyl iodide, and the resulting solution was heated at 50°C for 6 h, during which time the solution turned dark brown. The volatiles were removed *in vacuo* and the residue was triturated with pentane and filtered through a plug of celite. Evaporation of the solvent under reduced pressure gave 1,1-bis(pentamethylcyclopentadieny) -3-cyclohexyltitanacyclobutane complex **71** in 95% yield (**eq. 26**). Complex **71** was spectroscopically homogeneous and identical to the authentic material [97].

The new one–pot method does not require the use of Grignard reagents and gives a single one product in near quantitative yield. This method has now been used for the synthesis of other titanacyclobutane complexes and it also gives good results.[146]

The detailed mechanism for this process is not very clear; one possible reason for the success of this modification is that the initial interaction of the allyl halide is with the Cp^*_2TiCl. Such interaction generates the Ti(IV) complexes $Cp^*_2TiX_2$ and $Cp^*_2Ti(IV)(\eta^3\text{–allyl})X$. These two complexes are subsequently reduced by SmI_2 to generate the corresponding Ti(III) complexes Cp^*_2TiX and $Cp^*_2Ti(III)(\eta^3\text{–allyl})$; the latter then undergoes the normal alkylation process to produce the titanacyclobutane complexes.



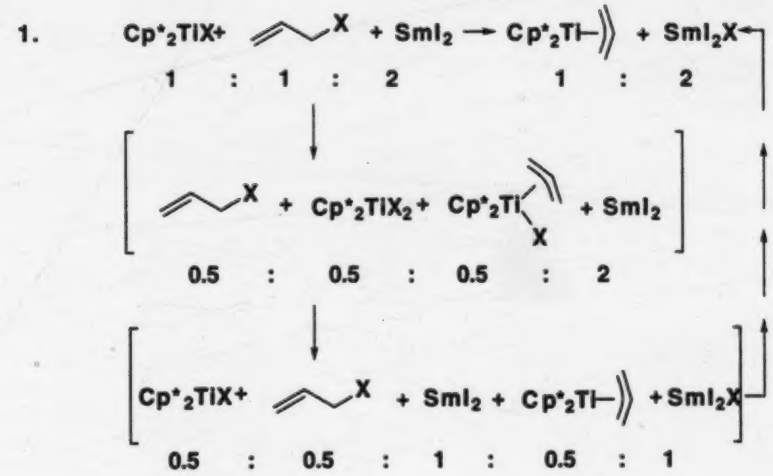
71

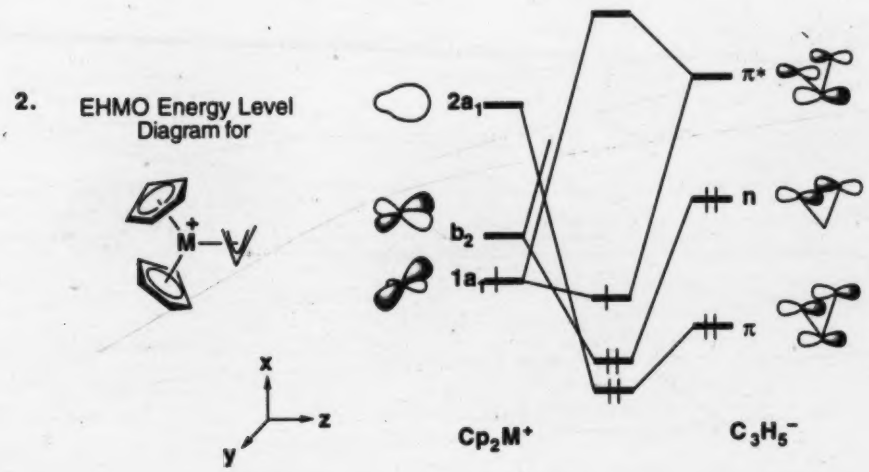
eq. 26

Mechanistically, this reaction can be divided into two stages: (i) generation of the allyl titanium(III) intermediate and (ii) alkyl radical formation and addition. Preliminary observations suggest that the mechanism of allyl complex formation proceeds by initial interaction of the allyl halide with Cp^*_2TiCl rather than with SmI_2. The addition of allyl bromide to a solution of Cp^*_2TiCl leads to the formation of the Ti(IV) complexes $Cp^*_2TiX_2$ (X = Cl and/or Br) and Ti(IV) allyl complexes (**Scheme 61, entry 1**). Reduction of both intermediates by SmI_2 must then occur at a slower rate, producing the titanium(III) allyl complex and regenerating Cp_2^*TiX, which then continues to react with the remaining allyl bromide. In the alkylation stage, it looks like that the alkyl radical is generated by direct reaction of alkyl halide and Cp_2^*TiX to produce the alkyl radical and the $Cp^*_2TiX_2$ again, and then the Ti(IV) dihalide $Cp^*_2TiX_2$ was reduced by SmI_2 back to the Ti(III) Cp_2^*TiX. Such process keep going untill all the allyl complexes are transformed to the corresponding titanacyclobutane products.

The unique central carbon selectivity can be explained by the reported EHMO energy level diagram.[139d-e] As showed in the scheme (**Scheme 61, entry 2**), the metal's $1a_1$ orbital and the allyl fragment's π^* orbital forms the single-occupied frontier molecular orbital (SOMO). It is the SOMO and the largest lobe on the central carbon of the allyl species to induce the central carbon free radical addition reactions.

Scheme 61





2. Intramolecular Free Radical Cyclizations of Titanium(III) Allyl and Propargyl Complexes

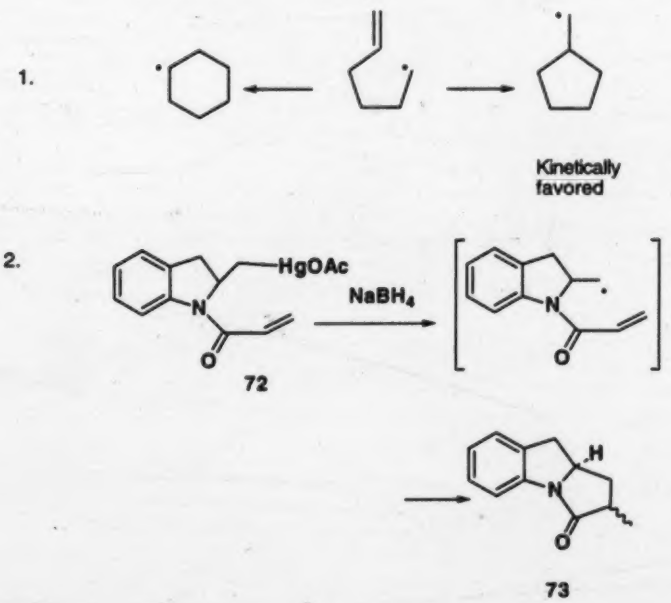
a. Introduction

The most common method for intramolecular cyclization reactions is through the carbocation intermediates. Free radical initiated cyclizations are also very interesting and have been developed rapidly in recent years. Radical-initiated cyclizations usually

kinetically favor 5-membered ring formation. One well-studied intramolecular free radical cyclization is the hex-5-enyl radical cyclization (**Scheme 62, entry 1**), which was investigated as early as the 1960's.[147] Later, Walling, Beckwith and Ingold[148] investigated the reaction mechanism in detail from a physical organic aspect. The most common explanation for this reaction selectivity is that the more favorable entropy factor leads to the 5-membered ring formation, although other factors such as stereochemistry and electronic effects may also effect the product formation.[149]

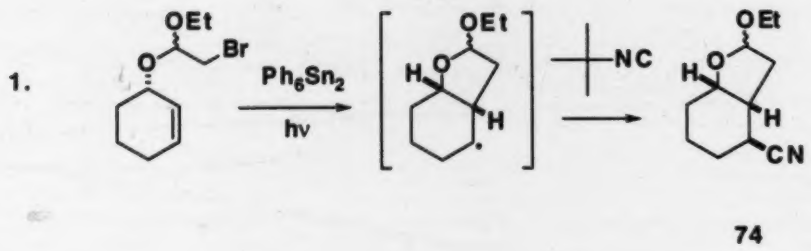
Among many synthetic applications that have been developed, one example is an organomercurial mediated intramolecular cyclization reaction reported by Danishefsky.[150] Reduction of organomercurial compound **72** with $NaBH_4$ produces a cyclized product mixture containing compound **73** in 45 % yield. (**Scheme 62, entry 2**)

Scheme 62

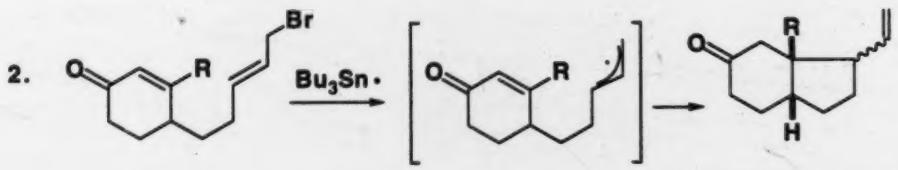


Stork[151] reported a tin–initiated intramolecular cyclization reaction. The radical intermediate in this reaction can be traped by excess isocyanide, as illustrated in **Scheme 63, entry 1**. The reaction introduces a chemically versatile cyano group into the cyclized molecule **74**. In another experiment, Stork showed that an allylic radical can also undergo an intramolecular cyclization reaction, giving the terminal olefin product **75** (**Scheme 63, entry 2**)[152]

Scheme 63



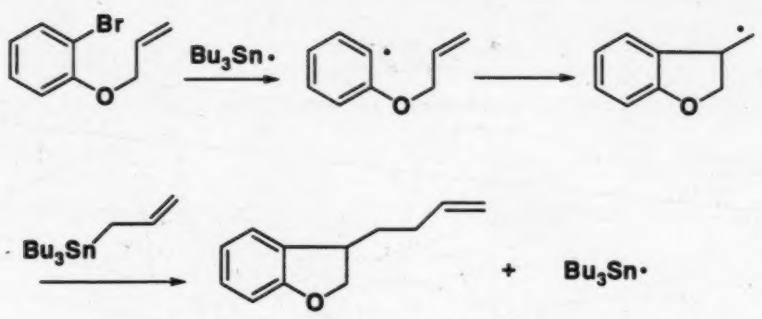
74



R = H, CH_3 **75**

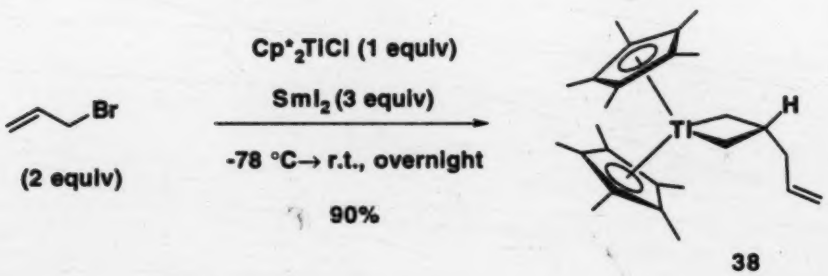
Moriya[153] reported successive intramolecular free radical cyclization and intermolecular free radical alkylation, a reaction sequence which occurred in one pot. The method has been applied to the synthesis of various monocyclic and bicyclic tetrahydrofurans from simple alkenes and allylic alcohols. (**Scheme 64**)

Scheme 64



Although there are many radical cyclizations in organic synthesis, some of them do not give good regioselectivity and stereoselectivity. It is interesting to develop similar cyclization process, using the titanium allyl and propargyl template to control the regioselectivity and stereoselectivity of the radical cyclization and use the steric and geometric constraints of metal coordination to favor the formation of medium to large ring systems.

In our previous investigations, Nomura found that treatment of Cp^*_2TiCl with two equivalents of allyl bromide in the presence of samarium (II) iodide yields β-allyltitanacyclobutane complex **38** in very high yield (**eq. 27**).[142] This reaction, however, is not successful using crotyl bromide as the substrate.



38

eq. 27

b. Intramolecular free radical cyclization of Ti(III) allyl complexes

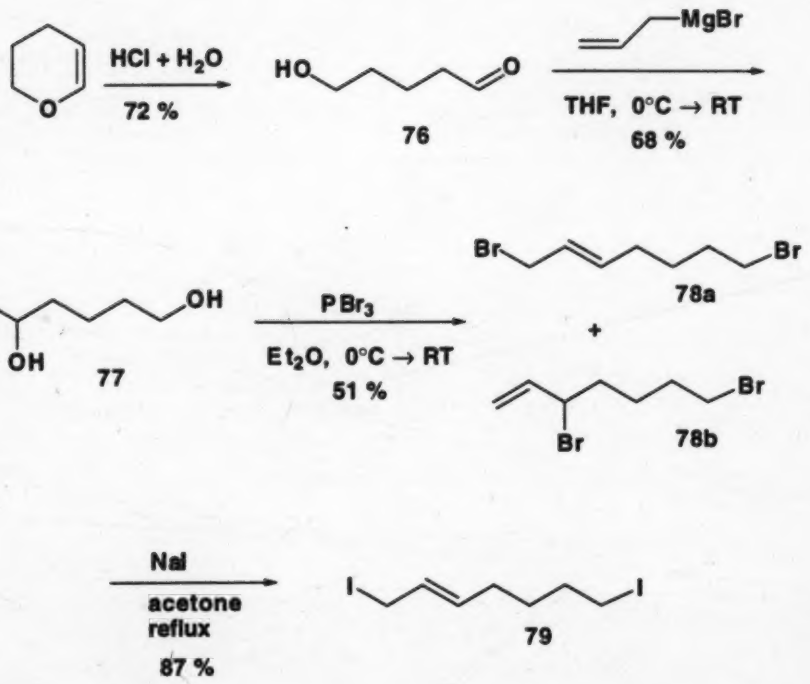
In an effort to develop the above methodology into an intramolecular free radical cyclization reaction, several bis(allyl bromide) substrates were synthesized and evaluated. As described in the previous section (*vide supra*), this reaction only works well for the six-member ring products **66a**; other ring size products could not be synthesized in high yield by this method (**Scheme 57, entries 1, 2, 3**).

We then attempted to extend this work, using a different type of substrate: the non–symmetrical dihalides, 1,7-dibromo-hept-2-ene and 1,7-diiodo-hept-2-ene. The two substrates were synthesized by the following straightforward route (**Scheme 65**). In the first step, acid hydrolysis of 2,3-dihydropyran produces the δ-hydroxyaldehyde **76** in good yield.[154] Reaction of compound **76** with an excess of vinyl magnesium bromide, followed by a standard aqueous work up, yields diol **77**, which was purified by distillation. Finally, double bromination of diol **77** with PBr_3 affords the desired product, 1,7-dibromo-hept-2-ene **78a** along with its allylic isomer **78b**. For conversion to the diiodide, the reaction of both **78a** and **78b** with sodium iodide in acetone gives 1,7-diiodo-hept-2-ene **79** (**Scheme 65**) with no evidence for any allylic isomer.

In the attempted cyclization, a solution of **78a** and **78b** in THF was mixed with Cp^*_2TiCl at low temperature (-35°C), whereupon the blue color of the solution changed immediately to red. Upon addition of a solution of SmI_2 in THF, the color changed back to blue. The resulting solution was allowed to warm to room temperature and maintained there for one hour, with the solution remaining dark blue. The reaction solution was then heated at 55°C for 24 h because there was no evident reaction observed. No desired product was formed.

In another experiment, $[^tBuCp_2TiCl]_2$ was used as the starting material, it was anticipated that the less electron rich ligand may result in a less reactive radical intermediate, which might avoid some undesired side reactions. In addition, the organic

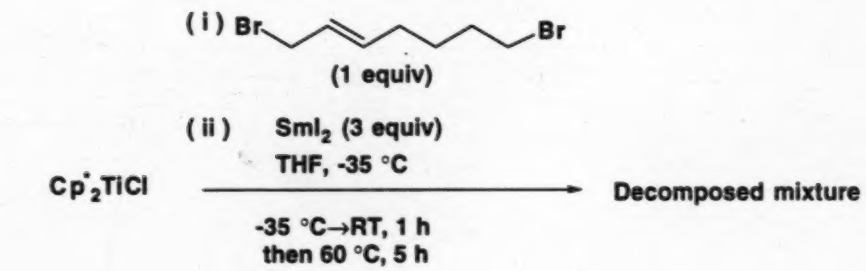
Scheme 65

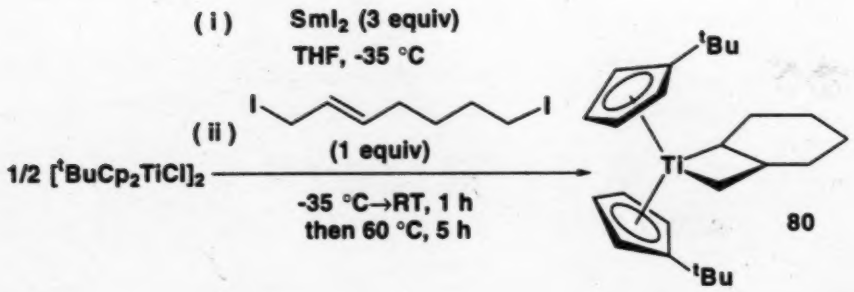


substrate was replaced by 1,7-diiodo-hept-2-ene in order to generate the primary radical more efficiently. Thus, a solution of $[^tBuCp_2TiCl]_2$ in THF at -35 °C was added to a solution of SmI_2 in THF at -35 °C. To this dark blue solution was added a solution of 1,7-diiodo-hept-2-ene in THF. The solution was shaken occasionally as the temperature rose to room temperature. After one hour at room temperature, the reaction mixture was heated at 60°C for 5 h. After work-up, the crude ^1H NMR spectrum revealed a multiplet at high field (δ -0.21), characteristic of the β-proton in bicyclic titanacyclobutane complexes[142] (*vide infra*). Other signals were consistent with the presence of inequivalent ^{t}BuCp ligands. These spectroscopic data suggest that the reaction mixture contains some

of the desired product (**Scheme 66**); however, this material decomposed during the separation process and further investigation was not pursued.

Scheme 66

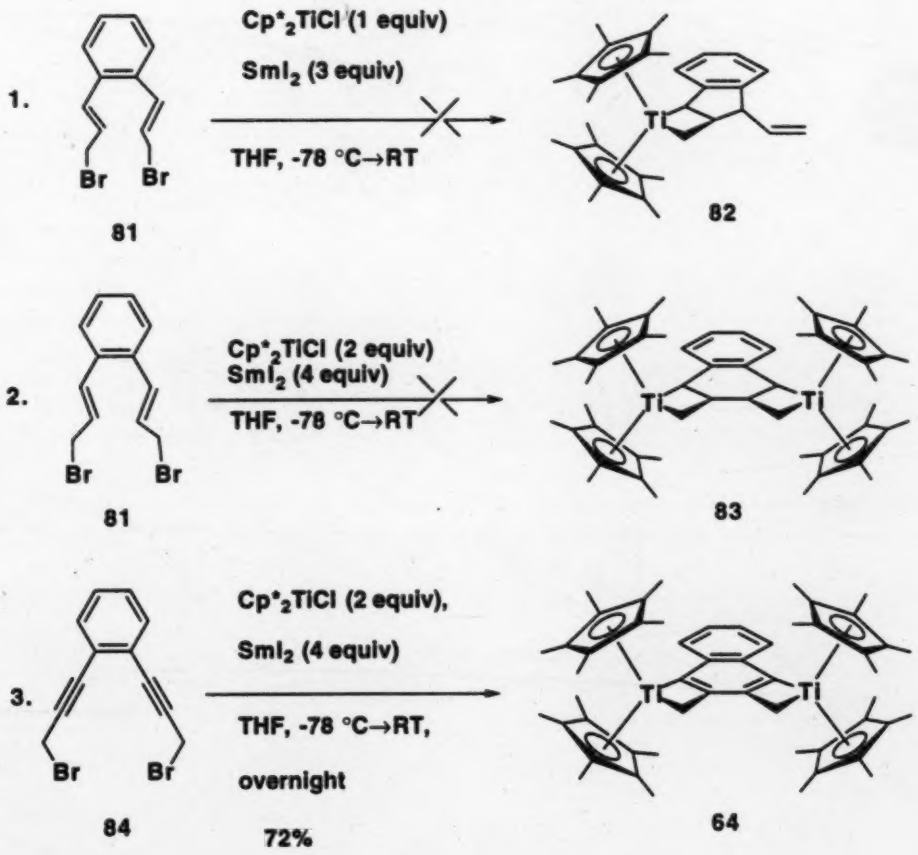




To introduce some rotational constraints into the bicyclic titanacyclobutane formation, benzylic bis(allyl) substrate **81** was synthesized by the reported procedure.[155-157] When **81** was treated with 1 equivalent of Cp^*_2TiCl and 3 equivalents of samarium(II) iodide in THF solution, the reaction produced only decomposition products; no desired five-membered ring product was formed (**Scheme 67, entry 1**). When **81** was treated with 2 equivalents of Cp^*_2TiCl and 4 equivalents of samarium(II) iodide in THF solution, the reaction also produced only decomposition products rather than the desired dimerization product **83** (**Scheme 67, entry 2**). One possible reason for the failure of substrate **81** to cyclize is the unfavorable steric interactions between the

substrate chain and the pentamethylcyclopentadienyl ligand in the titanocene allyl intermediate. By way of comparison, in the titanium(III) propargyl chemistry, when bis(propargyl) substrate **84** was treated with 2 equivalents of Cp^*_2TiCl and 4 equivalents of samarium(II) iodide, dimerization product **64** was produced in good yield (**Scheme 56, entry 2**).[141]

Scheme 67



c. Intramolecular free radical cyclization of Ti(III) propargyl complexes

As described in the previous section, Ogoshi's investigation determined that when the seven-carbon chain propargyl bromide substrate **67** is treated with Cp^*_2TiCl in the

presence of SmI_2, the six-membered ring bicyclic titanacyclobutene complex **68** is formed in quantitative yield (**eq. 21,** *vide supra).* In order to investigate the scope of this intramolecular propargyl cyclization, to develop general and practical new methodology for intramolecular radical cyclization, and to compare the reactivity of titanium(III) propargyl complexes with that of titanium(III) allyl complexes, other chain length analogous were targeted. We particularly wanted to know whether this method could be used for the preparation of seven-membered ring and eight-membered ring bicyclic titanacyclobutene complexes because neither of the corresponding bicyclic titanacyclobutane complexes could be made by this cyclization. Should these ring size be accessible, then we proposed to evaluate even larger ring synthesis as well. The more strained bicyclic five–membered ring bicyclic complex will also be investigated.

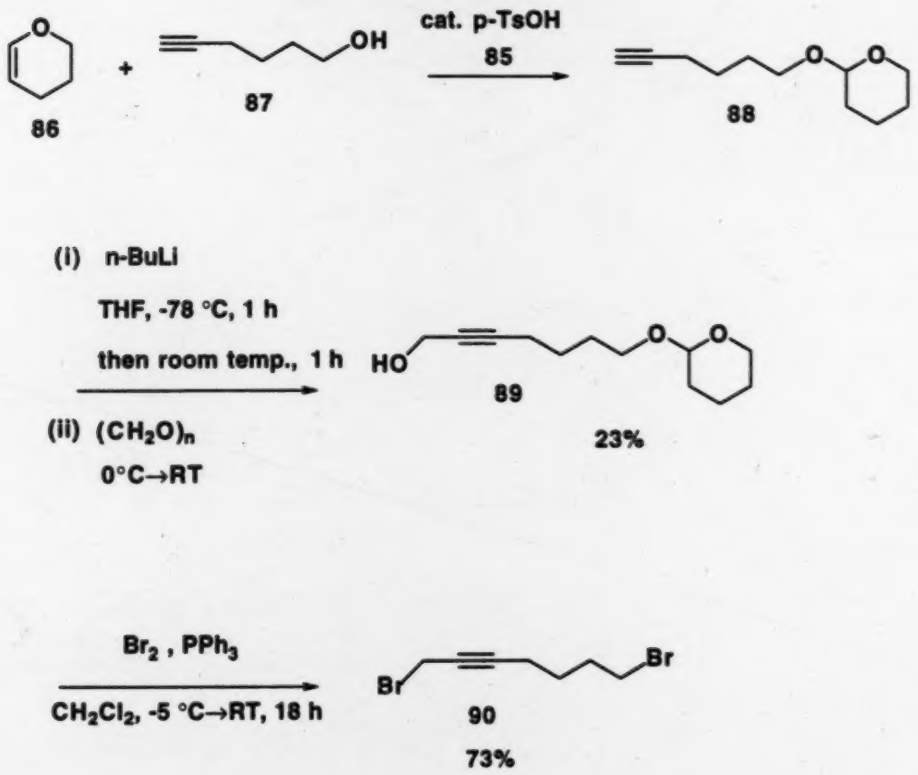
1. Substrate synthesis

The first problem to address was the substrate synthesis. In the previous synthesis developed by Ogoshi,[141] the seven-carbon propargyl bromide substrate 1,7-dibromo-2-heptyne **90** was synthesized by the following route (**Scheme 68**). This synthesis started with commercially available 5-hexyne-1-ol **87**. After THP protection, the terminal alkyne **88** was treated with butyllithium and paraformaldehyde to produce the substituted propargyl alcohol **89**. Subsequent bromination using bromine and triphenylphosphine yielded the target dibromide **90**. This general method has some drawbacks: the yield in the formylation step is low, the starting 5-hexyne-1-ol is very expensive, and the corresponding extended analogous 6-heptyne-1-ol and longer chain substrates are not commercially available. We needed to develop a more convenient method to synthesize the desired substrates.

Tiege had previously prepared a bis(propargyl bromide) substrate by the following route (**Scheme 69**).[158] By analyzing this synthesis, we thought that if the THP protected propargyl alcohol was treated with one equivalent of an alkyl dibromide,

the reaction could produce a monosubstituted alkylation product. Bromination of this product under the same conditions would produce the desired products efficiently even if the alkylation selectivity was low. Thus, the following synthesis was tested (**Scheme 70**)

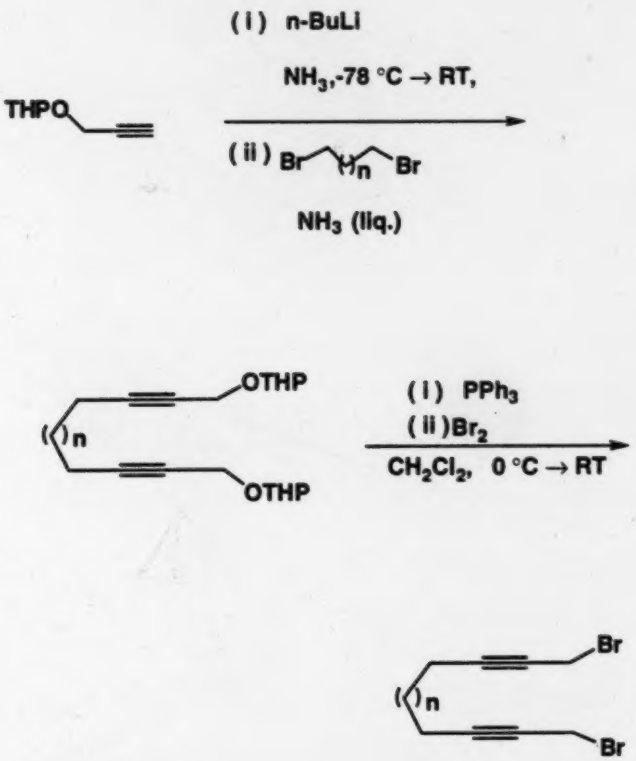
Scheme 68



Using this method, the entire series of desired compounds were synthesized. The results are listed in **Table 8**. This method requires fewer steps, gives higher yields, and all of the starting materials are commercially available and inexpensive. Although the yields in alkylation steps are not very high, the bromination step gives very good yields. The identification of these simple products was based on analysis of the spectroscopic

data. Characteristic signals can be found in the ^{1}H NMR spectra: the propargyl protons (H1) in these compounds appear as a narrow triplet at the lowest field in the spectrum, the H4 protons appear as triplet of triplets, and the terminal -CH_2Br protons appear downfield as normal triplets. In 1,9-dibromo-non-2-yne **93**, for example, the ^{1}H NMR spectrum

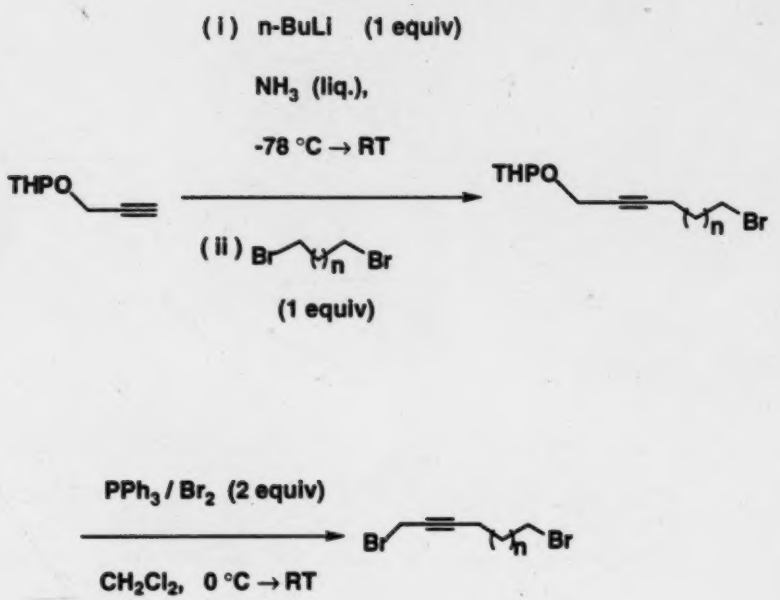
Scheme 69



shows characteristic signals for the propargyl protons at δ 3.92 (t, J = 2.3 Hz, 2 H), the terminal methylene protons at δ 3.40 (t, J = 6.8 Hz, 2 H), and the H4 protons at δ 2.24 (tt, J = 6.8; 2.3 Hz, 2 H). The remaining signals and integrations are consistent with the assigned structure. The ^{13}C NMR spectrum fully supports this structural assignment,

revealing the two alkyne carbons at δ 88.0 and 75.6 and halomethylene carbon signals at δ 33.8 and 32.6. High resolution mass spectrometry confirms the elemental composition

Scheme 70



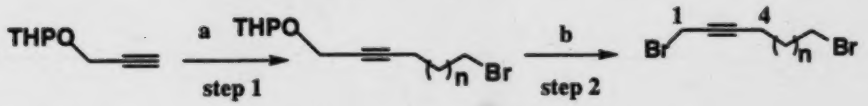
of $C_9H_{14}Br_2$. The remaining analogous **91**, **92**, **94**, and **95** gave similar spectroscopic data; with the assignments based on a similar analysis. These compounds were then used for the investigation of intramolecular free radical cyclization reactions to give bicyclic titanacyclobutenes.

2. Intramolecular bicyclization reactions

The investigation began with the synthesis of five-membered ring complex **96**. Thus, 1,6-dibromo-hex-2-yne **91** was treated with one equivalent of Cp^*_2TiCl and three equivalents of samarium(II) iodide at -78 °C under an inert atmosphere. The resulting

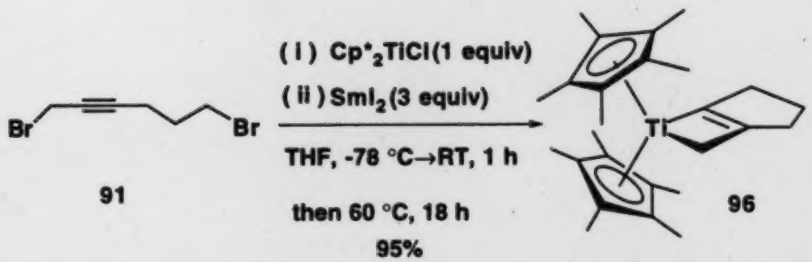
blue solution was allowed to warm to room temperature and then heated at 60 °C for 18 h. A brown-red solution was obtained. After evaporation of the solvent, the residue was triturated with pentane and then filtered through celite. Evaporation of the solvent afforded a clean product, 6,6-bis(pentamethylcyclopentadienyl)-titanabicyclo[3.2.0]hept-1(5)-ene **96**, in 95 % yield (**eq. 28**).

Table 8. Synthesis data for compounds 91 - 95



No.	n	time (h) step 1	yield (%) step1	time (h) step 2	yield (%) step2
91	1	3	25	20	86
92	3	3	63	20	91
93	4	4	51	12	93
94	5	4	54	12	86
95	6	3	54	20	90

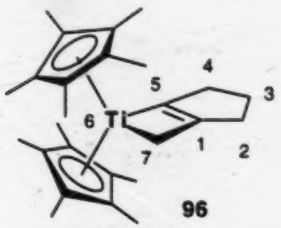
Conditions: a. (i) n–BuLi (1 equiv), NH_3 (liq.), -78°C→RT. (ii) 1, n+2 dibromoalkane. b. PPh_3/Br_2 (2 equiv), CH_2Cl_2, 0°C→RT



eq. 28

Assignment of the structure follows from a comprehensive analysis of the spectroscopic data (**Table 9**). The ^{1}H NMR spectrum indicates the signals for the α-proton at δ 2.06, which was confirmed in the two dimensional HMQC and HMBC spectra. In the HMQC spectrum, this proton is correlated to the C7 carbon downfield

Table 9. Spectroscopic data for complex 96



96

.^{1}H NMR (600 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, COSY)	^{1}H-^{1}H GCOSY (600 MHz, C_6D_6, each correlation listed only once)	^{13}C {^{1}H} NMR (75 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, COSY)
δ 2.83 (m, 2 H, H4), 2.47 (t, J = 7.3 Hz, 2 H, H2), 2.11 (quintet, J = 7.3 Hz, 2 H, H3), 2.06 (m, 2 H, H7), 1.69 (br s, 30 H, C_5Me_5).	δ 2.83 (H4) ↔ 2.47 (H2, weak), 2.11 (H3), 2.06 (H7, weak); 2.47 (H2) ↔ 2.11 (H3), 2.06 (H7, weak).	δ 230.0 (C5), 117.6 ($\underline{C}_5Me_5$), 110.8 (C1), 69.3 (C7), 40.4 (C4), 34.0 (C2), 30.0 (C3), 12.0 ($C_5\underline{Me}_5$).

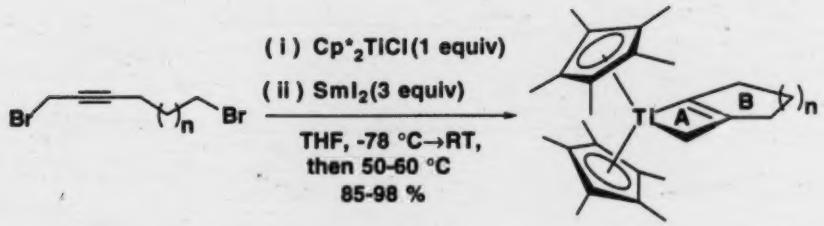
Table 9 continued.

HMQC (300 MHz, coupled, C_6D_6)	HMBC (600 MHz, C_6D_6, selected data only)	HRMS (*m/z*)
δ 69.3 (C7) ↔ δ 2.06 (J_{C-H} = 150.3 Hz, H7); δ 40.4 (C4) ↔ δ 2.83 (J_{C-H} = 150.3 Hz, H4); δ 34.0 (C2) ↔ δ 2.47 (J_{C-H} = 141.0 Hz, H2); δ 30.0 (C3) ↔ δ 2.11 (J_{C-H} = 151.9 Hz, H3); δ 12.0 (C5Me5) ↔ δ 1.69 (J_{C-H} =124.0 Hz, $C_5(CH_3)_5$).	δ 2.47 (H2) ↔ δ 30.0 (C3), 40.4 (C4, weak), 110.8 (C1), 230.0 (C5, weak); δ 2.11 (H3) ↔ δ 34.0 (C2), 40.4 (C4), 110.8 (C1), 230.0 (C5, weak); δ 2.06 (H7) ↔ δ 34.0 (C2).	calcd. *m/z* for $C_{26}H_{38}Ti$ 398.2453, found 398.2424.

at δ 69.3. The ^{13}C NMR spectrum showed characteristic signals for the presence of a titanacyclobutene moiety, with the C5 carbon signal appearing at δ 230.0 and the C1 carbon signal at δ 110.8, similar to other known titanacyclobutene complexes.[141] The ^1H-^1H GCOSY, HMQC and HMBC spectroscopic data fully support this assignment **(Table 9)**.

To examine the generality of this potentially useful cyclization process, 7-10 membered ring complex synthesis was investigated. Thus, one equivalent of Cp^*_2TiCl and three equivalents of samarium(II) iodide were treated with the corresponding propargyl substrates **92 - 95**, giving the desired bicyclic titanacyclobutene products **97 - 100** in high yield. The results are listed in **Table 10**:

Table 10. Synthesis data for complexes 97–100

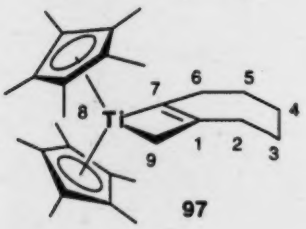


n	product	temperature (final) (°C)	time (h)	yield (%)
3	**97**	50	16	98
4	**98**	60	24	96
5	**99**	60	24	92
6	**100**	60	12	85

Table 10 shows that all of the reactions go to completion within 24 h at 50 °C - 60 °C with excellent yields. This methodology allows formation of a wide range of bicyclic complexes ranging from five to ten–membered ring systems. The isolation of these products is very convenient. In most cases, the products can be isolated and purified by pentane extraction followed by celite filtration under inert atmosphere. Only the nine- and ten–membered ring products required further purification by recrystallization.

The structural assignments of complex **97 - 100** follow from a comprehensive analysis of the spectroscopic data similar to that described for complex **96**. For the seven-membered ring complex **97**, the spectroscopic data are listed in **Table 11**.

Table 11. Spectroscopic data for complex 97



97

.^{1}H NMR (600 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, COSY)	^{1}H-^{1}H GCOSY (600 MHz, C_6D_6, each correlation listed only once)	^{13}C {^{1}H} NMR (75 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, COSY)
δ 2.43 (br s, 2 H, H6), 2.36 (s, 2 H, H9), 2.32 (m, 2 H, H2), 1.72 (br s, 30 H, C5(C<u>H</u>3)5), 1.68 (m, 2 H, H4), 1.58-1.66 (m, 4 H, H3, H5).	δ 2.43 (H6) ↔ 1.59 (H5), 2.36 (H9), 2.32- (H2); 2.32 (H2) ↔ 1.64 (H3).	δ 210.9 (C7), 117.6 (<u>C</u>$_5$Me$_5$), 104.5 (C1), 83.9(C9), 35.7 (C6), 34.7 (C2), 32.0 (C4), 30.4 (C5), 28.9 (C3), 12.0 (C$_5$<u>Me</u>$_5$).

Table 11 continued.

HMQC (600 MHz, decoupled, C_6D_6)	HMBC (600 MHz, C_6D_6, selected data only)	HRMS (*m/z*)
δ 83.9 (C9) ↔ δ 2.36 (H9); δ 35.7 (C6) ↔ δ 2.43 (H6); δ 34.7 (C2) ↔ δ 2.32 (H2); δ 32.0 (C4) ↔ δ 1.68 (H4); δ 30.4 (C5) ↔ δ 1.59(H5); δ 28.9 (C3) ↔ δ 1.63(H3).	δ 2.43 (H6) ↔ δ 30.4 (C5), 32.0 (C4), 104.5 (C1), 210.9 (C7); δ 2.36 (H9) ↔ δ 104.5 (C1), 210.9 (C7); δ 2.32 (H2) ↔ δ 28.9 (C3), 32.0 (C4), 104.5 (C1), 210.9 (C7).	*m/z* for $C_{28}H_{42}Ti$ calcd. 426.2766, found 426.2771.

The ^{13}C NMR gave characteristic signals for the presence of the titanacyclobutene moiety. The C7 sp^2 α–carbon signal appears at δ 210.9, more shielded compared to the δ 230.0 signal in complex **96**. The β-carbon of the titanacyclobutene appears at δ 104.5, also slightly more shielded than the β-carbon in complex **96** (δ 110.8). The sp^3 α-carbon, however, is deshielded and appears at δ 83.9, while this carbon in complex **96** appears at δ 69.3. The results show that the more strained ring is deshielded and all the larger rings are "normal." This trend is maintained for complexes **98–100**. The B-ring carbon connectivity was assigned by comprehensive analysis of the two dimensional NMR spectra. The HMBC spectrum indicates that both H2 and H6 are correlated to both C1 and C7 and that H6 is correlated to C5 and C4, while H2 is correlated to C3 and C4 but not C5. This means that both C2 and C6 are in allylic positions because both carbons are correlated to the two double bond carbons. C6 is connected to C5, C2 is connected to C3, and both C3 and C5 are connected to C4. This connectivity was confirmed by the

GCOSY spectrum, which shows the homoallylic coupling between H9 and H6, but no coupling between H9 and the cross–conjugated position H2. The remaining spectroscopic data support this assignment (**Table 11**).

Assignments of the eight–, nine–, and ten–membered ring titanacyclobutene complexes **98**, **99**, and **100** are based on similar analysis. The key ^{13}C NMR spectroscopic data are listed in **Table 12**.

In contrast to normal free radical cyclization reactions,[149,159] in which the large size ring compounds are difficult to make, here the titanium mediated intramolecular free radical cyclizations yield five- to ten–membered ring complexes in high yield. This is most probably due to the fixed geometry of the propargyl moiety, which limits the rotational freedom of the alkyl chain and enhances the cyclization. This effect is similar to the Thorpe–Ingold effect.[160,161]

Table 12.

^{13}C NMR Resonances of titanacyclobutene complexes 98–100

98

99

100

	98 δ (ppm)	**99** δ (ppm)	**100** δ (ppm)
$\underline{C}_5(CH_3)_5$	117.9	118.0	117.8
$C_5(\underline{C}H_3)_5$	12.1	12.5	12.1
sp^2 α-C	212.0	215.5	212.4,
sp^3 α-C	82.4	80.7	78.4
sp^2 β-C	105.0	105.1	105.7
B ring signals $-(CH_2)_n-$	33.6, 33.2, 30.4, 27.7, 27.3, 26.1.	34.7, 33.0, 29.5, 28.5, 26.9, 26.4, 22.7.	35.1, 32.8, 32.3, 31.6, 31.4, 31.1, 30.3, 29.5.

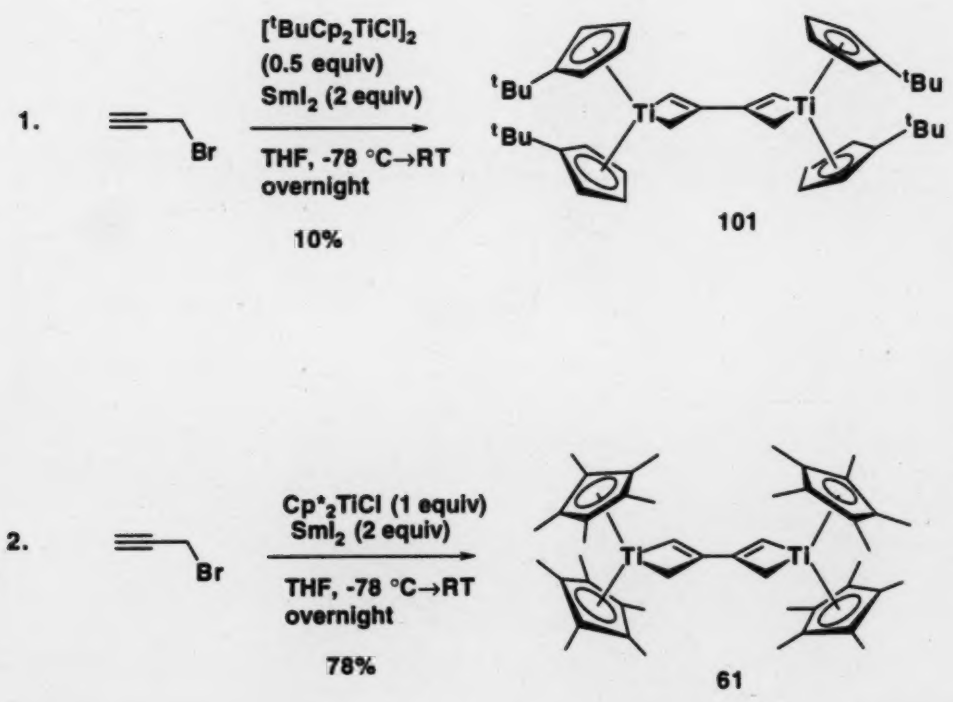
3. Radical Additions of Titanium (III) Propargyl Complexes Using Cp and ^{t}BuCp Templates.

a. Investigation of ^{t}BuCp Templates

To further investigate the steric and electronic features of the ancillary ligand set which affect the addition of organic radicals to the η^3-propargyl ligand, the *tert*-butylcyclopentadienyl ancillary ligand set was investigated. This ligand is more electron rich than the unsubstituted cyclopentadienyl ligand and it is less sterically bulky than the Cp* ligand. Therefore, in contrast to Cp* ligand, the ^{t}BuCp ligand provides a more open environment about the metal center. Another reason to investigate the use of the ^{t}BuCp ligand is that although the Cp* ligand provides an efficient route for the radical addition of titanium(III) propargyl complexes, it has two major limitations: the Cp*H ligand is expensive either to make or to buy, and the titanacyclobutene products are too stable to undergo many insertion reactions and demetallation reactions, principally because the metal is sterically inaccessible to external reagents. These unfavorable factors limit its application in organic synthesis. In a preliminary investigation, Ogoshi found that when $[^t BuCp_2TiCl]_2$ was treated with one equivalent of propargyl bromide and two equivalents samarium(II) iodide, dimerization product **101** was obtained, but only in 10 % yield (**Scheme 71, entry 1**). Under identical conditions, the Cp* ligand produces the corresponding dimerization product **61** in 78 % yield (**Scheme 71, entry 2**).

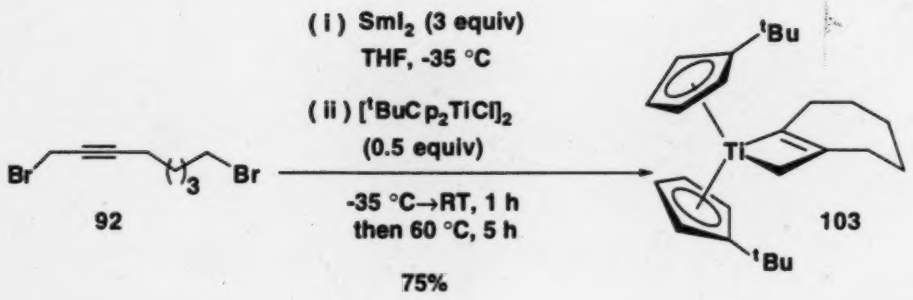
From the investigation of intramolecular radical cyclization reactions of titanium(III) propargyl complexes, we found that the bis(Cp*) bicyclic complexes **97 - 100** are thermally very stable. For example, when each complex was heated at 60 °C overnight, no decomposition was observed. Attempted ketone insertion, however, does not occur in these complexes.

Scheme 71



These observations led us to investigate the same cyclization reaction with the ^{t}BuCp ligand set. Thus, 1,8-dibromo-oct-2-yne **92** was treated with 0.5 equivalents of $[^{t}BuCp_2TiCl]_2$ and three equivalents of samarium(II) iodide at -35 °C. The reaction mixture was allowed to warm to room temperature and then heated at 60°C for 5 h until the color of the reaction solution changed from blue to dark brown. After work-up, the desired bicyclic seven–membered ring product **103** was obtained in 75 % yield **(eq. 29)**.

With the exception of the ancillary ligand set, the spectroscopic data for the complex **103** is very similar to the corresponding Cp* coordinated complex **97**. The ^{1}H NMR spectrum indicates the presence of the ^{t}BuCp ligand set, with four narrow multiplets at δ 5.88, 5.56, 5.38 and 5.34. Integrals shows that each narrow multiplet

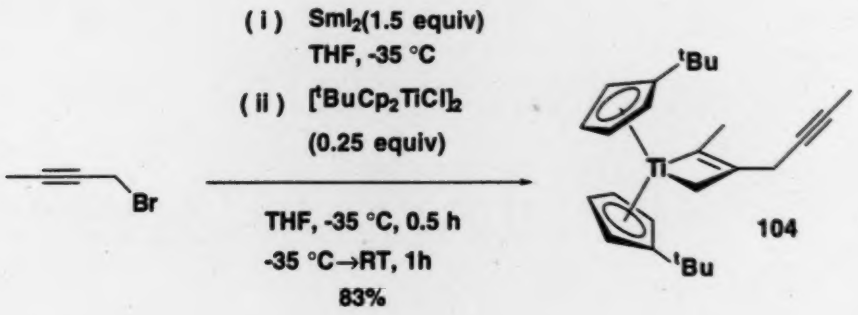


eq. 29

represents two protons. The characteristic signal for the tert-butyl group appears as a broad singlet at δ 1.15, with an integral of 18 protons. The $^{13}C\{^1H\}$ NMR spectrum reveals the signal for the sp^2 α-carbon of the titanacyclobutene at δ 217.2, similar to the Cp* analogue, which appears at δ 210.9. The signal for the β-carbon of the titanacyclobutene ring appears at δ 97.6, while in Cp* analogue this carbon appears at δ 104.5. The sp^3 α-carbon of the titanacyclobutene ring appears at δ 79.4, very close to that in the Cp* analogue at δ 83.9. The remaining signals and spectroscopic data are fully consistent with the assigned structure.

As a result of the success of the intramolecular radical cyclization reaction, several intermolecular radical addition reactions were also investigated. This evaluation started with the addition of a stabilized radical. Thus, two equivalents of 2-butynyl bromide were added to a solution of three equivalents of samarium (II) iodide and 0.5 equivalents of $[^tBuCp_2TiCl]_2$ in THF at -35 °C. The resulting solution was kept at -35 °C for 0.5 h and then allowed to warm to room temperature. After remaining at room temperature for one hour, the desired complex **104** was obtained in 83% isolated yield (**eq. 30**). The assignment of titanacyclobutene complex **104** follows from analysis of the spectroscopic data and comparison to the analogous product in the Cp* series, prepared by Ogoshi.[141]

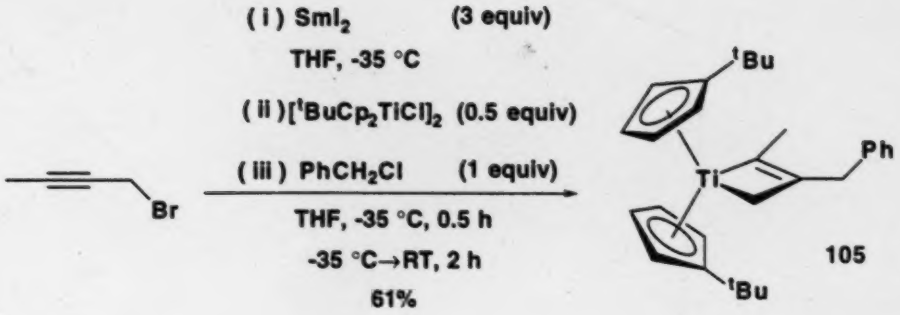
The ^1H NMR spectrum reveals the presence of the ^{t}BuCp ligand set, with the characteristic four narrow multiplets at δ 5.85 (m, 2 H), 5.68 (m, 2 H), 5.56 (m, 2 H), and 5.35 (m, 2 H), along with a broad singlet at δ 1.13, integrating to 18 protons.



eq. 30

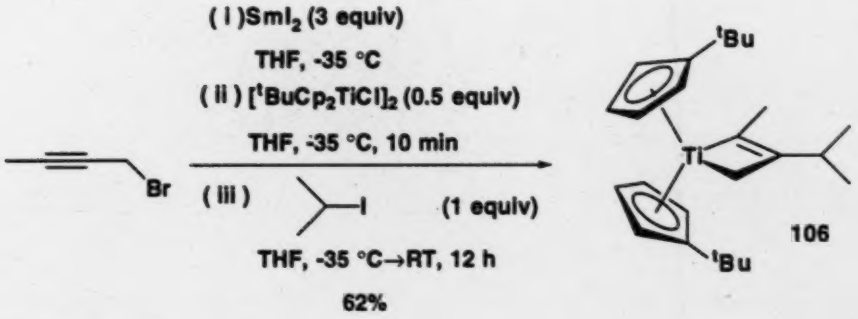
The ^{13}C {^1H} NMR spectrum reveals a typical signal for the sp^2 α-carbon of the titanacyclobutene ring at δ 209.2 and a signal for the β-carbon at δ 93.9. The sp^3 α-carbon of titanacyclobutene appears at δ 77.8 and two sp carbon signals of the butynyl moiety appear at δ 72.3 and 68.5. The remaining signals and spectroscopic data are consistent with the assigned structure.

In another experiment with a stabilized radical, $[^t BuCp_2TiCl]_2$ (0.5 equiv.) was treated with three equivalents of samarium(II) iodide at -35 °C, followed by a combined solution of one equivalent of 2-butynyl bromide and one equivalent of benzyl chloride in THF. The resulting solution was shaken and kept at -35 °C for a short time (0.5 h) and then allowed to warm to room temperature. After remaining at room temperature for 2 h, complex **105** was obtained as a red oil in 61% yield after standard work–up (**eq. 31**). Structural assignment of complex **105** was accomplished in a manner similar to that of **104** and the product was very similar spectroscopically to the analogous Cp* complex.[141]



eq. 31

In order to test the generality of the ^{t}BuCp mediated intermolecular radical addition, the reaction of an unstabilized radical was considered. Thus, 0.5 equivalents of $[^t BuCp_2TiCl]_2$ were mixed with three equivalents of samarium(II) iodide and one equivalent of 2-butynyl bromide at -35 °C. The resulting solution was kept at -35 °C for a short time (10 min), then a solution of isopropyl iodide in THF was added at -35 °C. The blue reaction mixture was allowed to warm to room temperature and remain for 12 h. After work-up, complex **106** was obtained in 62% isolated yield (**eq. 32**). Structure assignment of complex **106** was accomplished in a manner similar to that described for



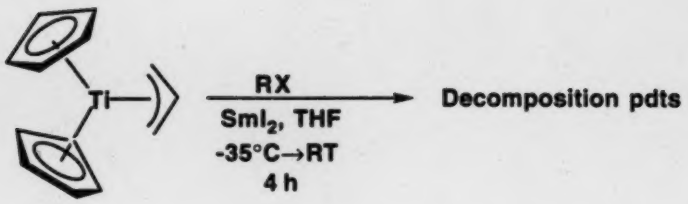
eq. 32

complex **104** and **105**. In ^1H NMR spectrum, the methylene protons on the titanacyclobutene ring appear as a narrow quartet at δ 3.08 (q, J_{obs} = 1.6 Hz, 2 H). This small coupling constant is a result of long range coupling from the α-methyl group, which was confirmed by the triplet at δ 2.16 (J = 1.6 Hz, 3H). The isopropyl moiety was identified by a septet signal at δ 2.79 (J = 6.8 Hz, 1 H) and a doublet at δ 0.96 (d, J = 6.8 Hz, 6 H).

In summary, the ^{t}BuCp ligand set provides a more convenient template for the preparation of both monocyclic and bicyclic titanacyclobutene complexes because the starting material is inexpensive and simple to make. Both intermolecular radical addition reactions and intramolecular radical cyclization reactions work well. This analysis also defines an unique property for this ligand set: it promotes radical coupling reactions easily, but it does not undergo the competitive dimerization reaction.

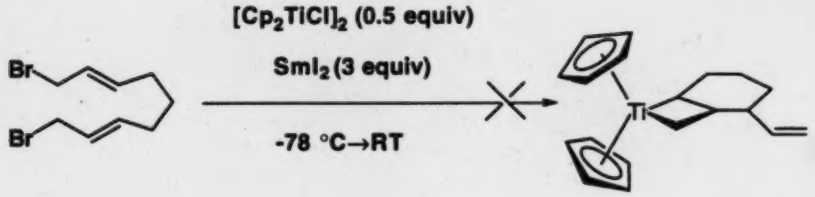
b. Investigation of cyclopentadienyl templates

The unsubstituted cyclopentadienyl ligand is one of the most important ligands in organometallic chemistry. Complexes of this ligand also have important applications in organic synthesis.[144,162-165] In order to apply this ligand to the titanium allyl and propargyl chemistry, our group has investigated many related reactions. In 1994, Casty treated $Cp_2Ti(\eta^3\text{-}C_3H_5)$ with an alkyl halide in the presence samarium (II) diiodide; no desired titanacyclobutane complex was formed (**eq. 33**).[96] When either tin or mercury reagents were used to generate organic radicals, the reaction still did not produce a titanacyclobutane complex.



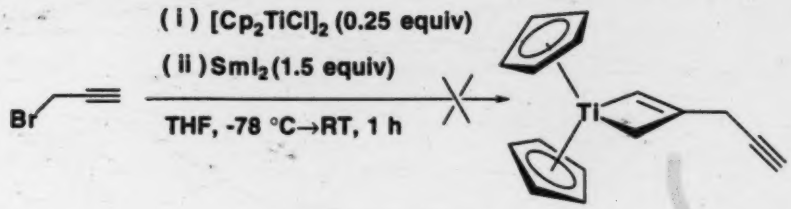
eq. 33

In 1995, Nomura treated the nine-carbon bis(allyl bromide) substrate with $[Cp_2TiCl]_2$ in the presence of samarium (II) diiodide. The reaction resulted in a complicated, unknown product mixture (**eq. 34**).



eq. 34

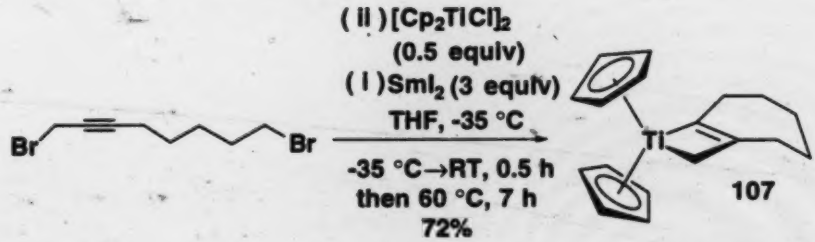
In 1997, Ogoshi treated $[Cp_2TiCl]_2$ with four equivalents of propargyl bromide and six equivalents of samarium (II) diiodide, but the reaction produced only a complex mixture of unidentified products; none of the desired titanacyclobutene complex was formed. (**eq. 35**).



Ogoshi, 1997

eq. 35

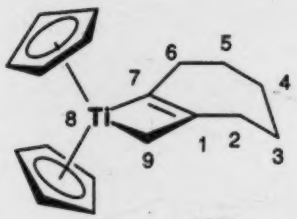
Nonetheless, in part because the starting material, $[Cp_2TiCl]_2$, is commercially available, the use of the Cp ligand set was re-investigated. Intramolecular radical cyclization reactions were initially investigated, because both the Cp* ligand and ^{t}BuCp ligand sets gave very stable products and we hoped that the intramolecularity of the cyclization would help to drive the reaction to a titanacyclobutene product. The use of a non–stabilized primary radical might also encourage the addition to occur more readily than Ogoshi's use of a propargyl radical. Thus, a solution of 1,8-dibromo-oct-2-yne in THF was added to a solution of $[Cp_2TiCl]_2$ and samarium(II) diiodide at -35 °C. The resulting blue solution was allowed to warm to room temperature and then heated at 60°C for 7 h until the color of the solution changed to dark brown. After work-up, the target complex **107** was obtained in a surprising 72 % yield (**eq. 36**).



eq. 36

Assignment of complex **107** follows from comprehensive analysis of the spectroscopic data (**Table 13**) and comparison to both Cp* and ^{t}BuCp analogous **97** and **103**.

Table 13. Spectroscopic data for complex 107.



107

^{1}H NMR (300 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, INAPT, COSY)	^{1}H-^{1}H GCOSY (300 MHz, C_6D_6, partial data only, each correlation listed only once)	^{13}C {^{1}H} NMR (75 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, INAPT, COSY)
δ 5.51 (S, 10 H, $C_5\underline{H}_5$), 3.32 (s, 2 H, H9), 2.52 (m, 2 H, H6), 1.99 (m, 2 H, H2), 1.59 (m, 2 H, H4), 1.50 (m, 2 H, H5), 1.40 (m, 2 H, H3).	δ 3.32 (H9) ↔ 2.52 (H6), 2.52 (H6) ↔ 1.50 (H5), 1.99 (H2) ↔1.40 (H3).	δ 219.9 (C7), 110.0 ($\underline{C}_5H_5$), 92.7 (C1), 82.8 (C9), 37.6 (C6), 32.6 (C2), 31.6 (C4), 28.6 (C5), 27.0 (C3).

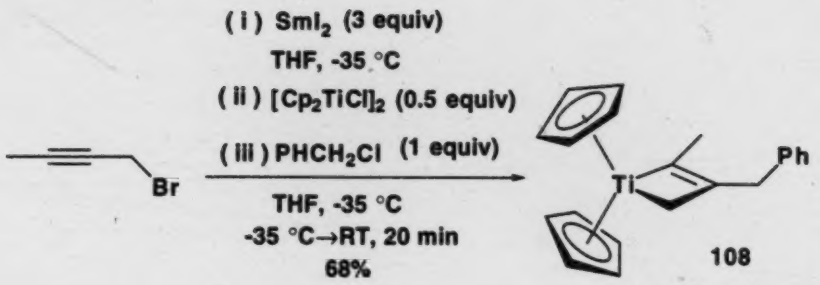
Table 13 continued.

HMQC (300 MHz, coupled, C_6D_6)	HMBC (300 MHz, C_6D_6, selected data only)	INAPT (300 MHz, C_6D_6)
δ 82.8 (C9) ↔ δ 3.31 (J_{C-H} = 137.6 Hz, H9); δ 37.6 (C6) ↔ δ 2.51 (J_{C-H} =118.8 Hz, H6); δ 32.6 (C2) ↔ δ 1.99 (J_{C-H} = 125.1 Hz, H2); δ 31.6 (C4) ↔ δ 1.59 (J_{C-H} 112.6 Hz, H4); 28.6 (C5) ↔ δ 1.50 (J_{C-H} = 131.3 Hz, H5); δ 27.0 (C3) ↔ δ 1.40 (J_{C-H} =118.8 Hz, H3); 110.0 ($\underline{C}_5H_5$) ↔ δ 5.51 (J_{C-H} = 113.8 Hz, $C_5\underline{H}_5$).	δ 3.32 (H9) ↔ δ 219.9 (C7), 92.7 (C1), 32.6 (C2); δ1.99 (H2) ↔ δ 219.9 (C7), 92.7 (C1), 82.8 (C9, weak), 31.6 (C4), 27.0 (C3); δ 1.59 (H4) ↔ δ 28.6 (C5) ; δ 1.50 (H5) ↔ δ 219.9 (C7), 37.6 (C6, weak), 31.6 (C4), 27.0 (C3); δ 1.40 (H3) ↔ δ 92.7 (C1, weak), 31.6 (C4), 28.6 (C5).	irridiate H9 at δ = 3.32, two carbon signals showed up: δ 219.9 (C7), 32.6 (C2).

The ^{1}H NMR spectrum indicates the signal for the α-methylene group (H9) at δ 3.32. This assignment was confirmed by HMQC, INAPT and HMBC spectrums. In the HMQC spectra, this proton is correlated to the signal at δ 82.8, consistant with the sp^3 α-carbon. In the INAPT experiment, when this proton was irradiated, two carbon signals were observed at δ 219.9 and 32.6, leading to the assignment of these two carbons as C7 and C2. In this particular case, C2 and C6 were thus rigorously differentiated, with the

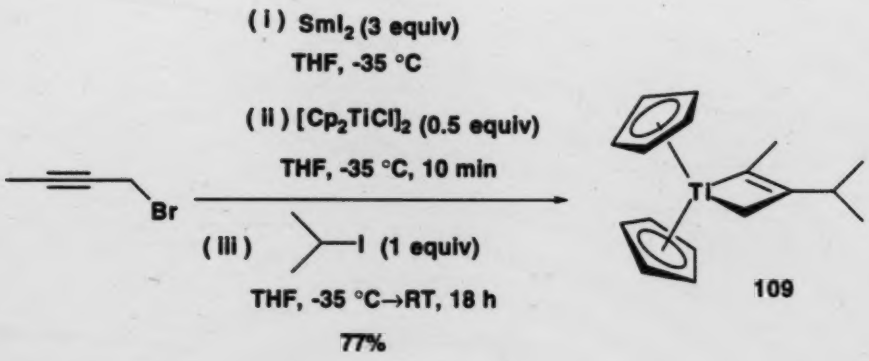
carbon at 32.6 connected to the β–carbon rather than the distant α–carbon. The HMBC spectrum confirms this connectivity, with H9 correlated to C1, C2 and C7. The COSY spectrum establishes the homoallylic coupling between H9 and H6. Both the COSY and HMBC spectra allow the full assignment of all ring proton and carbon signals. Finally, the ^{13}C NMR spectrum again shows characteristic signals for the presence of the titanacyclobutene moiety: the C7-carbon at δ 219.9, the C1 signal at δ 92.7, and the C9 signal at δ 82.8. The remaining signals and spectroscopic data are consistent with the assigned structure.

Not anticipating much success, intermolecular radical addition reactions were also investigated. Thus, two equivalents of 2-butynyl bromide were treated with a mixture of three equivalents of samarium (II) iodide and 0.5 equivalents of $[Cp_2TiCl]_2$ in THF solution at -35 °C. No characterizable product was obtained, consistant with Ogoshi's results. In another experiment, however, the $[Cp_2TiCl]_2$ (0.5 equiv.) was treated with three equivalents of samarium(II) iodide, first at -35 °C, and then a solution containing one equivalent of 2-butynyl bromide and one equivalent of benzyl chloride in THF was added at -35 °C. The resulting solution was allowed to warm to room temperature. After remaining at room temperature for 20 minutes, complex **108** was obtained in a 68% isolated yield (**eq. 37**). The assignment of complex **108** was based on analysis of spectroscopic data and comparison to the analogous Cp^*[141] and ^{t}BuCp complexes **105** (*vide supra*). The signal for benzyl methylene protons appears as a singlet at δ 3.23. The methylene protons in the titanacyclobutene ring appear as a narrow quartet at δ 3.05 (q, J = 1.6 Hz, 2H), owing to the small coupling constant to the methyl protons, as confirmed by the narrow triplet at δ 2.22 (t, J = 1.6 Hz, 3H). In the $^{13}C\{^1H\}$ NMR spectrum, the signal for the sp^2 α-carbon of the titanacyclobutene ring appears at δ 211.1 and the signal for the β-carbon appears at δ 90.9. The sp^3 α-carbon of the titanacyclobutene ring appears at δ 75.7. The remaining signals and spectroscopic data are consistent with the assigned structure.



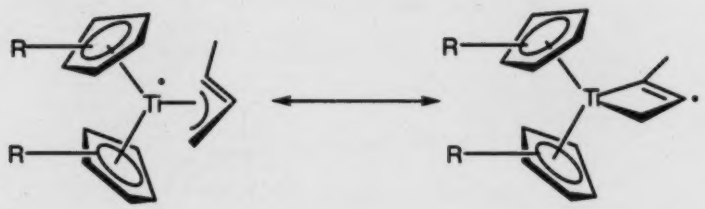
eq. 37

With this unexpected result, the addition of an unstabilized radical was investigated by using isopropyl iodide. Thus, to a solution of $[Cp_2TiCl]_2$ in THF at –35 °C was added a solution of samarium(II) iodide and 2-butynyl bromide in THF. After 10 minutes at -35 °C, isopropyl iodide was added and the resulting solution was allowed to warm to room temperature and stand for18 h. After work–up, complex **109** was obtained in 77 % yield (**eq. 38**). Structural assignment of complex **109** was accomplished in a manner similar to that of complex **108**.



eq. 38

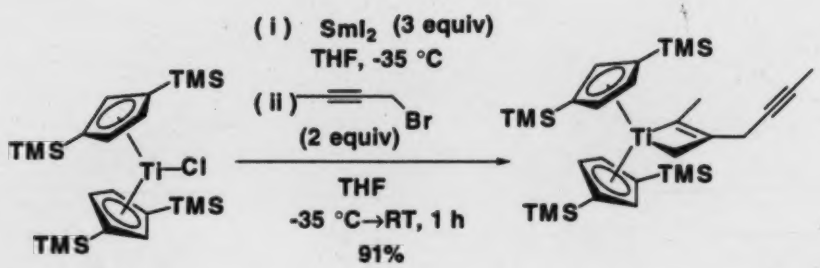
By comparing the reactivity of the Cp*, ^{t}BuCp, and Cp ligand sets, it is clear that the Cp* ligand set is the most reactive for the radical addition reaction. The Cp ligand set showed the lowest reactivity, with no addition of the propargyl radical observed. These observations suggest that the electron density requirement is important for central carbon alkylation, indicating that the high electron density at the metal center increases the metal d→π*propargyl back-bonding. The enhanced back-bonding increases preference for η^3-coordination and provides a greater delocalization of the odd-electron density onto the central carbon of the propargyl ligand. This gives the central carbon more radical character, activating the complex toward radical alkylation and enhancing the central carbon regioselectivity, as illustrated by the resonance structure shown in (**eq. 39**)



eq. 39

In order to help confirm this speculation, the reactivity of the bis(TMS-Cp) ligand was briefly investigated. This ligand is much more electron rich and more hindered than the Cp ligand. Thus, treatment of titanocene chloride **110**[166] with samarium (II) iodide and propargyl bromide affords complex **111** in high yield (91%) (**eq. 40**). The structure assignment of complex **111** is based on the analysis of spectroscopic data, which is closely analogous to other complexes with this structure. The ^{1}H NMR spectrum indicates the presence of characteristic signals for the bis(TMS-Cp) ligand, which appear as three singlets at δ 6.43, 5.95 and 5.88, and the 36 protons from the TMS groups appear as a broad singlet at δ 0.20. Two different methylene groups on the

titanacyclobutene and propargyl positions appear as singlets at δ 3.48 and 2.87. The two methyl groups appear at δ 2.20 (s, 3 H) and 1.66 (s, 3 H). The $^{13}C\{^1H\}$ NMR spectrum is fully consistent with the assigned structure.



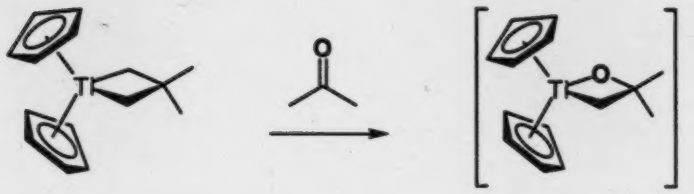
110 111

eq. 40

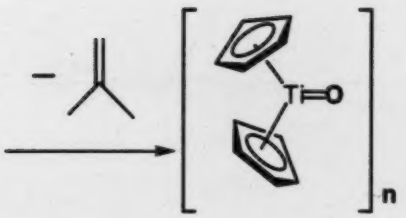
c. Functionallization of titanacyclobutenes

To investigate the reactivity of titanacyclobutene complexes and develop a new methodology for the efficient synthesis of useful organic molecules, a preliminary investigation into the functionallization of titanacyclobutene complexes was undertaken. Grubbs and co-workers reported extensively on the reactivity of both titanacyclobutane and titanacyclobutene complexes.[107-109,118,167-169] Bis(cyclopentadienyl)titanacyclobutane complex **112**, for example, reacts with acetone to form an unstable oxatitanacyclobutane complex **113**. This complex reacts further to form the corresponding olefin (a "Wittig"–like product) and the polymeric titanocene oxide **114** (**eq. 41**).[165]

In 1988, Grubbs demonstrated that the reaction of bis(cyclopentadienyl)titanacyclobutene complex **115** with acetone produces an insertion



112 113



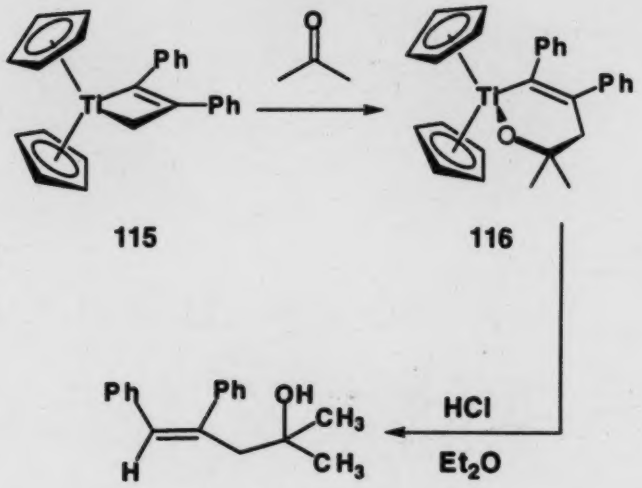
114

eq. 41

product **116**. In this reaction, the acetone inserts into the titanium-alkyl bond. Complex **116** undergoes a demetallation reaction under acidic conditions to produce the homoallylic alcohol **117 (Scheme 72).** This insertion reaction has limitations; according to Grubbs, it requires that the α-position of the titanacyclobutene has a phenyl substituent. When the α-position is substituted with an alkyl group, the reaction forms an unstable product.[167]

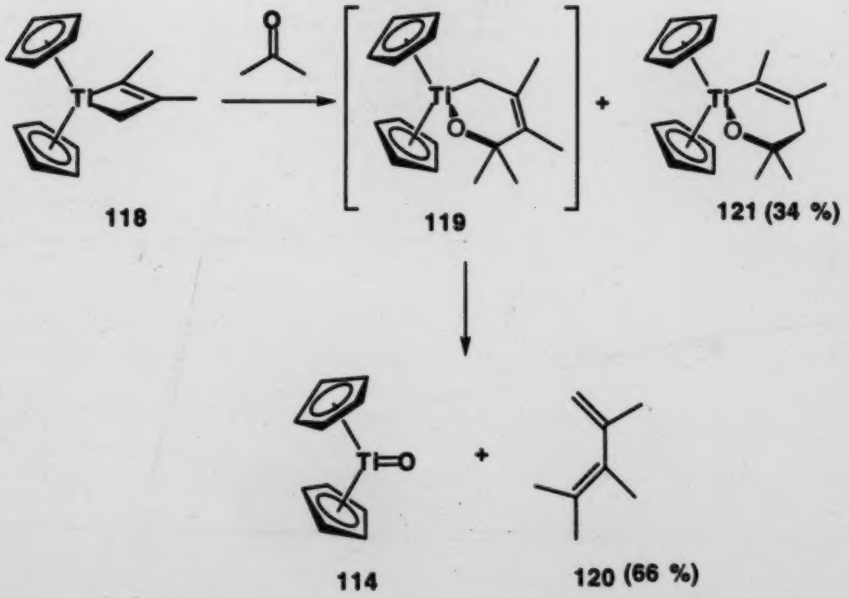
Several years later, Doxsee and coworkers carefully reinvestigated the ketone insertion reaction of bis(cyclopentadienyl)titanacyclobutene complexes. They found that when the α-position of the titanacyclobutene has an alkyl substituent, the ketone is inserted into both the titanium-vinyl and the titanium-alkyl bonds. The product distribution depends on the steric bulk of the alkyl group. For example, when complex **118** is treated with acetone, the reaction gives 34% of the alkyl insertion product **121** and 66% of an organic

Scheme 72



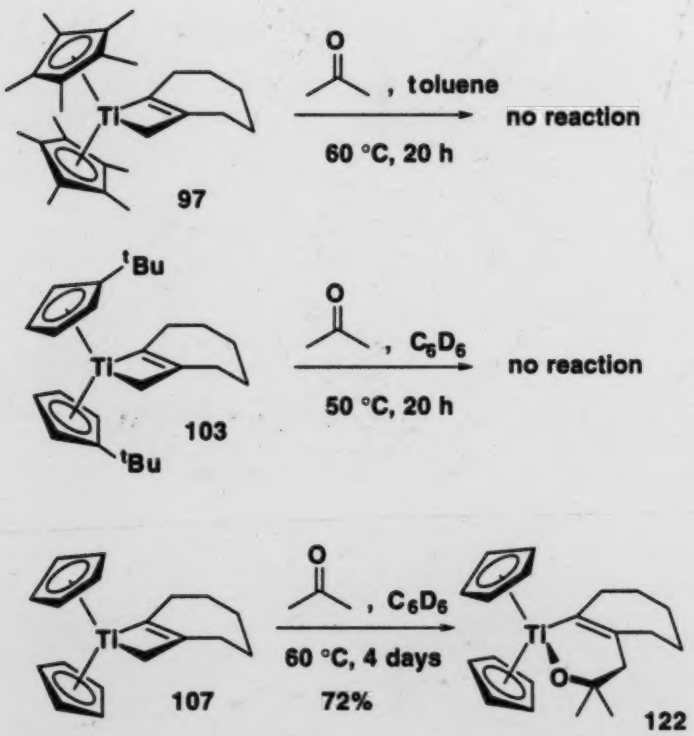
diene **120**, derived from insertion into the vinyl-metal bond. Diene **120** is the decomposition product of intermediate **119** (**Scheme 73**).[118]

Scheme 73



The previous investigations of the ketone insertion reactions use simple monocyclic titanacycles. The reactivity of bicyclic titanacycles have been sparsely investigated, partly because until now, there has been no practical method to synthesize such compounds. We selected the 7-member ring bicyclic complexes **97**, **103** and **107** with decreasingly bulky ancillary ligands for a brief investigation of ketone insertion reactions. When a solution of pentamethylcyclopentadienyl complex **97** and excess acetone in toluene was heated in a bomb for a prolonged time, no reaction occurred. Both starting materials were recovered unchanged. Under similar reaction conditions, complex **103** also does not react with

Scheme 74

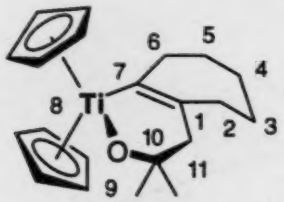


acetone. While steric effects are probably dominant, anther possible reason for this lack of reactivity is that the electron rich ligand can induce stronger titanium-carbon bonds in the titanacyclobutene complex, making the complexes more stable (*vide supra*). When the Cp complex **107** is heated with excess acetone, a slow reaction was observed, and after four days, the insertion product **122** was obtained in 72% yield (**Scheme 74, entry 3**). The product shows that the ketone inserted selectively into the titanium-alkyl bond.

The structural assignment of complex **122** was based on a comprehensive analysis of the spectroscopic data (**Table 14**). The ^{1}H NMR spectrum indicates that the signal for the H11 proton now appears at δ 2.29, shifted only slightly upfield from its corresponding position in complex **107**. This assignment was confirmed by two dimensional HMQC and HMBC experiments. In the HMQC spectrum, these protons are correlated to the C11 carbon at δ 60.9. In the HMBC spectrum, H11 is correlated to C1, C10, C6, C7 and methyl carbon signals at δ 133.5, 86.8, 39.2, 191.6, and 28.0 ppm. The six protons from the two methyl groups appear as a singlet at δ 1.10. The COSY spectrum establishes that the methylene proton H11 is coupled to the homoallylic methylene proton H6. The ^{13}C NMR spectrum also gives some characteristic signals. The C7 carbon signal appears at δ 191.6, the Cp signal appears at δ 112.3. The large shift of the C1 carbon signal from its previous position as the β–carbon in **107** (92.7) to the new position at δ 133.5 in **122** is especially noteworthy. The remaining signals and spectroscopic data are consistent with the assigned structure.

After the ketone insertion reaction was accomplished, our attention was directed towards acidic demetallation to give an organic product. Thus, complex **122** was taken up in ether and placed in a glass bomb. Dry HCl gas was introduced into the solution at 0 °C and bubbled through for 5 minutes, giving 1-cyclohept-1-enyl-2-methylpropane-2-ol **123** in 83% yield (**eq. 42**) after aqueous work–up and flash column purification. The assignment of the homo-allylic alcohol **123** was based on analysis and comparison of the spectroscopic data with that in the literature.[117]

Table 14. Spectroscopic data for complex 122

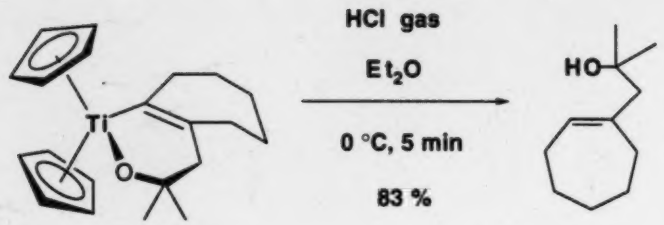


122

^{1}H NMR (300 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, COSY)	^{1}H-^{1}H GCOSY (300 MHz, C_6D_6, each correlation listed only once)	^{13}C {^{1}H} NMR (75 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, COSY)
δ 5.83 (S, 10 H, $C_5\underline{H}_5$), 2.29 (s, 2 H, H11), 2.22 (m, 2 H, H2), 2.02 (m, 2 H, H6), 1.80 (m, 2 H, H4) 1.62 (m, 2 H, H5), 1.50 (m, 2 H, H3), 1.10 (s, 6H, CH_3).	δ 2.29 (H11) ↔ 2.02 (H6); 2.22 (H2) ↔ 1.50(H3), 2.02 (H6) ↔1.62 (H5); 1.80 (H4) ↔ 1.62(H5), 1.50 (H3).	δ 191.6 (C7), 133.5 (C1), 112.3 ($\underline{C}_5H_5$,), 86.8 (C10), 60.9 (C11), 39.2 (C6), 37.4 (C2), 33.0 (C4), 29.2 (C3), 28.0 (CH_3), 26.8 (C5).

Table 14 continued.

HMQC (300 MHz, coupled, C_6D_6)	HMBC (300 MHz, C_6D_6, selected data only)	HRMS
112.3 ($\underline{C}_5H_5$) ↔ δ 5.83 (J_{C-H} = 170.0 Hz, $C_5\underline{H}_5$); δ 60.9 (C11) ↔ δ 2.29 (J_{C-H} =125.1 Hz, H11); δ 39.2 (C6) ↔ δ 2.02 (J_{C-H} = 120.9 Hz, H6); δ 37.4 (C2) ↔ δ 2.22 (J_{C-H} = 125.1 Hz, H2); δ 33.0 (C4) ↔ δ 1.80 (J_{C-H} = 158 Hz, H4); δ 29.2 (C3) ↔ δ 1.50 (J_{C-H} = 141.8 Hz, H3); δ 28.0 ($\underline{C}H3$) ↔ δ 1.10 (J_{C-H} = 125.1 Hz, $C\underline{H}3$); δ 26.8 (C5) ↔ δ 1.62 (J_{C-H} 150.1 Hz, H5).	δ 2.29 (H11) ↔ δ 191.5 (C7), 133.5 (C1), 86.8 (C10); 39.1 (C6), 28.0 ($\underline{C}H_3$); δ 2.22 (H2) ↔ δ 191.5 (C7), 133.5 (C1), 60.9 (C11, weak), 33.0 (C4), 26.8 (C5, weak); δ 2.02 (H6) ↔ δ 191.5 (C7), 133.5 (C1), 33.0 (C4, weak); δ 1.80 (H4) ↔ δ 39.2 (C6) ; δ 1.50 (H3) ↔ δ 133.5 (C1); δ 1.10 ($C\underline{H}_3$) ↔ δ 86.8 (C10), 60.9 (C11), 28.0 ($\underline{C}H_3$).	calcd. *m/z* for $C_{21}H_{28}TiO$ 344.1619, found 344.1628 .

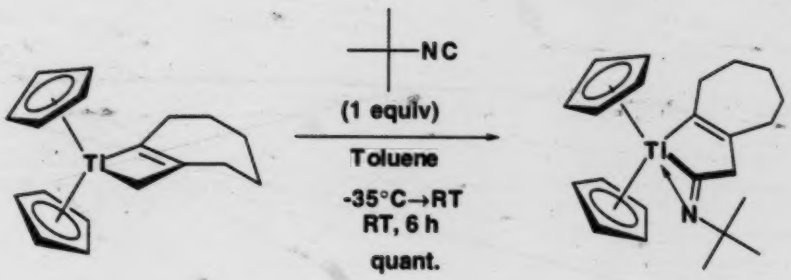


122 123

eq. 42

As reported by Nicolaou,[170] medium–ring homoallyllic alcohols such as compound **123** are important intermediates for macrolide antibiotic synthesis. An earlier preparation of **123** was reported by Masamune[171] and the most recent synthesis of compound **123** was reported by Das, who provided detailed spectroscopic data.[117]

An isocyanide insertion reaction has also been investigated. Hicks and Buchwald synthesized iminocyclopentenes from the cyclocondensation of an enyne with an isonitrile, this process involves the insertions of isonitrile into a substituted titanacyclopentene complex.[173] Berg and Petersen reported insertions of *tert*-butyl isocyanide into a 1–sila–3–zirconacyclobutane complex.[172] Our group has also investigated isonitrile insertion reactions of titanacyclobutane complexes.[174] To investigate the isonitrile insertion reaction of complex **107**, the complex was treated with one equivalent of tert-butyl isocyanide in toluene at -35°C. The resulting solution was warmed slowly to room temperature and stirred at room temperature for 6 h. Iminoacyl insertion product **124** was formed in quantitative yield (**eq. 43**). The structural assignment of complex **124** follows from analysis of the spectroscopic data and comparison to similar complexes.[172,173] The tert-butyl moiety was identified by a singlet at δ 0.92 in the ^{1}H NMR spectrum, but all other signals are similar to the those of starting material.



107 124

eq. 43

The $^{13}C\{^1H\}$ NMR spectrum indicates more substantial changes. The signal for the vinylic α-carbon of the titanacycle appears at δ 225.6 and the iminoacyl α-carbon of the titanacycle appears at δ 190.5, similar to other iminoacyl resonances.[172-174] The signal for the sp^2 β-carbon of the titanacycle appears at δ 143.3, again shifted downfield from the starting material. The remaining signals and spectroscopic data are consistent with the assigned structure.

Although further insertion and demetallation reactions have not been pursued, these results show that the Cp_2Ti template has considerable potential for future applications in organic synthesis

D Conclusions

We have investigated free radical addition and cyclization reactions of titanium(III) propargyl complexes and titanium(III) allyl complexes. A new method for the synthesis of titanacyclobutane complexes has been established, using Cp^*_2TiCl as the starting material. Titanacyclobutane complexes can thus be made conveniently in one pot. In the propargyl chemistry, research on the intramolecular free radical cyclization reaction

established that the full series of bicyclic complexes with ring sizes ranging from five to ten can be made in high yield. We also investigated ancillary ligand effects and expanded the range of complexes that support titanacyclobutene formation via radical addition. Our results reveal that both bis(Cp*) and bis(TMSCp) ligand sets form titanacyclobutene complexes in high yield, while the less electron rich bis(^{t}BuCp) and bis(Cp) ligand sets also work reasonably well, giving titanacyclobutene complexes in slightly lower yields. These observations indicate that relatively electron-rich ancillary ligand sets facilitate radical addition but for propargyl chemistry, even the bis(Cp)Ti template can be used successfully. It does not appear as though steric hindered ligands inhibit the alkylation reaction based on the fact that the bis(TMSCp) ligand set forms titanacyclobutene complex in high yield. In the functionallization reactions, however, we found that only the cyclopentadienyl titanacyclobutene complexes undergo insertion reactions readily, and the ketone insertion reaction produces useful organic molecules after demetallation under acidic conditions. Future work in this area will be focused on preparing more substituted ring systems and those which contain more functionality. Other insertion reactions will also be investigated, to provide more practical utility for organic synthesis.

III. EXPERIMENTAL

General: All air-sensitive manipulations were conducted under a nitrogen atmosphere using standard Schlenk or drybox techniques. Infrared (IR) spectra were recorded on Perkin-Elmer 1420, 298, and 283, Pye Unicam PU9522, and Nicolet 7199 Fourier transform spectrophotometers, and are reported in reciprocal wave numbers (cm^{-1}) calibrated to the 1601 cm^{-1} absorption of polystyrene. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Varian INOVA300, Varian INOVA600, Varian UNITY500, Bruker AM-200 (for ^{31}P and ^{1}H), Bruker AM-360, Bruker AM-300 [300 MHz (^{1}H), 75 MHz (^{13}C)] and Bruker AM-400 [400 MHz (^{1}H) and 100 MHz (^{13}C)] spectrometers. Chemical shifts are reported in parts per million (ppm, δ) relative to TMS (^{1}H and ^{13}C) or H_3PO_4 (^{31}P) and coupling constants are reported in hertz (Hz). Unless stated otherwise, NMR spectra were obtained at 23 °C and coupling constants reported as J refer to J_{HH} for ^{1}H NMR spectra and J_{CH} for ^{13}C NMR spectra or could not be unambiguously assigned due to the presence of multiple spin active atoms in close proximity. Coupling constants are reported to 0.1 hertz, which is within the limits of instrumental precision, but these values are normally accurate only to within ± 0.5 hertz. Multiplicities are reported as observed. 2–D NMR abbreviation used are: HMQC (Heteronuclear Multiple Quantum Correlation), HMBC (Heteronuclear Multiple Bond Correlation), COSY (correlated spectroscopy), INAPT (Intensive Nuclei Assigned by Polarization Transfer). High Resolution Mass Spectra (HRMS) were obtained on a Kratos MS-80RFA spectrometer operating at 40 eV. Abbreviations used in the assignment of metallacyclobutane resonances are "α" (positions adjacent to the metal) and "β" (position distal to the metal).

All hydrogenation reactions above atmospheric pressure were performed in a Fischer & Porter medium pressure glass bottle (20-75 psi), or in a stainless steel Parr

autoclave (75-1500 psi), each equipped with Swagelok Quick-connects and pressure gauges.

Analytical thin layer chromatography (TLC) was performed on precoated glassbacked silica gel plates, (E. Merck 60 F_{254}, 0.25mm) and visualized by irradiation with UV light, 14% ethanolic phosphomolybdic acid heat, 6% ethanolic vanillin heat, aqueous $KMnO_4$-NaOH-K_2CO_3, or iodine supported on silica gel. Flash column chromatographic separations were performed using silica gel 60 (0.040-0.063 mm, E. Merck). Celite filtrations were performed using a plug of Hyflo Super Cel (Fisher) over glass wool in disposable pipets or alone on sintered glass funnels under vacuum. Cylindrical medium-walled Pyrex vessels equipped with Kontes k-826510 Teflon vacuum stopcocks are referred to as glass bombs.

Materials: Unless indicated otherwise, solvents and reagents were purchased from commercial vendors, distilled or passed down a plug of neutral alumina, and degassed prior to use by repeated freeze-pump-thaw cycles on a vacuum line. Benzene, hexanes, pentane, tetrahydrofuran, and diethyl ether were purified by distillation from sodium or potassium benzophenone ketyl. Dichloromethane was distilled from calcium hydride and deoxygenated prior to use. *tert*-Butanol was distilled from sodium, deaerated, and stored under nitrogen. $[(Ph_3P)CuH]_6$ was prepared by the current literature method.[44]

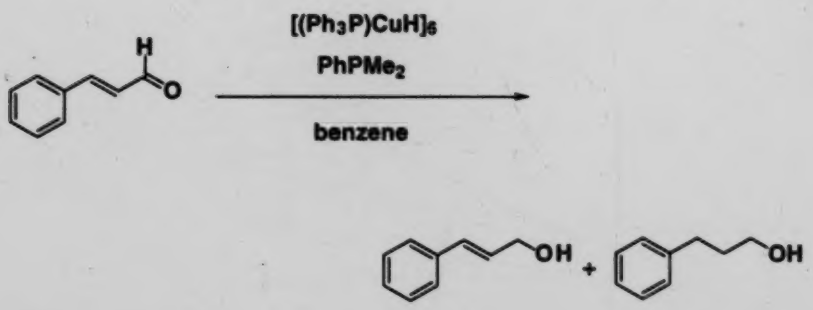
PART ONE: CHEMOSELECTIVE CATALYTIC HYDROGENATION OF α, β–UNSATURATED ALDEHYDES AND KETONES TO ALLYLIC ALCOHOLS USING SOLUBLE COPPER(I) HYDRIDES

A. Catalytic Hydrogenation of α,β-Unsaturated Aldehydes and Ketones Using Me_2PPh–stabilized Cu(I) Hydride and Hydrogen.

Evaluation of Catalytic Reaction Conditions

1. Solvent Effects.

a. Benzene solvent.



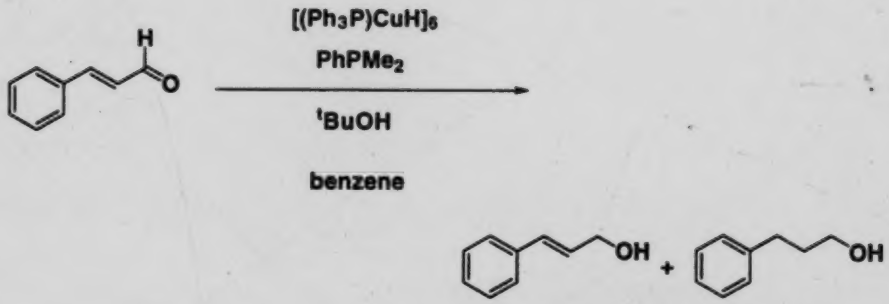
In the glove box, $[(Ph_3P)CuH]_6$ (0.026 g, 0.0135 mmol, 5 mol% Cu), benzene (0.4-0.8 M in substrate), dimethylphenylphosphine (0.067 g, 0.49 mmol), and *tert*-butanol (0.12 g, 1.62 mmol) were placed into a small vial. *Trans* -cinnamaldehyde (0.043 g, 0.32 mmol) was then added and the mixture was transferred into a 25 mL Schlenk flask which contained a magnetic stirbar. An additional 0.2 mL of benzene was added to the

vial to rinse any remaining material into the Schlenk flask. The flask was capped, removed from the glovebox, and filled with one atm of hydrogen after one "freeze-pump-thaw" degassing cycle. The solution was stirred under H_2 at room temperature for one day. TLC analysis showed that most of the starting material was not consumed. After three days, the mixture solution was opened to air. Analysis of the crude mixture by ^1H NMR spectroscopy showed that the major compound is the starting material along with some allylic alcohol product (< 17%) and other unknown material; no saturated alcohol product was observed. The allylic alcohol product was identified by comparison to an authentic sample prepared by the reduction of *trans*-cinnamaldehyde with $NaBH_4/CeCl_3$[61] : ^1H NMR (300 MHz, C_6D_6) δ 1.45 (s, 1 H), 3.92 (dd, J = 2.8, 0.8 Hz, 2 H), 6.05 (dt, J = 15.5, 5.5 Hz, 1 H), 6.42 (dt, J = 15.5, 1.5 Hz, 1 H), 6.93-7.23 (m, 5 H). The saturated alcohol product was checked by comparison to an authentic sample prepared by catalytic hydrogenation of the authentic allylic alcohol over Pd/C at 100 psi hydrogen pressure in ethyl acetate: ^1H NMR (200 MHz, C_6D_6) δ 1.62 (m, 2H), 2.50 (t, J = 7.5 Hz, 2 H), 3.28 (t, J = 6.5 Hz, 2 H), 6.95-7.30 (m, 5 H).

b. THF solvent.

Following the above procedure, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), THF (0.4-0.8 M in substrate), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.024 g, 0.33 mmol) were placed into a small vial. *Trans* -cinnamaldehyde (0.043 g, 0.32 mmol) was then added. The resulting reaction mixture was hydrogenated under one atmosphere of hydrogen at room temperature for two days. TLC analysis showed that most of the starting material was not consumed. After three days, no more conversion was observed.

2. *tert*- Butanol Dependency.



In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), benzene (0.4-0.8 M in substrate), dimethylphenylphosphine (0.013 g, 0.097 mmol), and *tert*-butanol (amount show below) were placed into a small vial. *Trans*-cinnamaldehyde (0.043 g, 0.32 mmol) was then added and the resulting solution was transferred into a 25 mL Schlenk flask, which contained a magnetic stirbar. An additional 0.2 mL of benzene was added to the vial to rinse any remaining material into the Schlenk flask. The flask was capped, removed from the glovebox, and filled with one atm of hydrogen after one "freeze-pump-thaw" degassing cycle. The solution was stirred under H_2 at room temperature for the indicated time (show below), after which the volatiles were removed under vacuum and the resulting crude product mixture was separated by flash column chromatography (eluting with $CHCl_3$) and analyzed by spectroscopy. This procedure was repeated four times with the concentration of added *tert*-butanol being varied; the amount of *tert*-butanol, the reaction time, and the allylic alcohol product yields are listed below.

Added *tert*-butanol Equivalents/Cu	Reaction time (h)	Allylic alcohol yield (%)
0	72	30
20	72	52
40	3.0	60
60	3.0	56

3. Dimethylphenylphosphine Dependency.

In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), benzene (0.4-0.8 M in substrate), dimethylphenylphosphine (amount show below), *tert*-butanol (0.048 g, 0.65 mmol) were placed into a small vial. *Trans*-cinnamaldehyde (0.043 g, 0.32 mmol) was then added and the mixture solution was transferred into a 25 mL Schlenk flask containing a magnetic stirbar. An additional 0.2 mL of benzene was added to the vial to rinse any remaining material into the Schlenk flask. The flask was capped, removed from the glovebox, and filled with one atm of hydrogen after one "freeze-pump-thaw" degassing cycle. The solution was stirred under H_2 at room temperature for the indicated time (time show below). The resulting reaction mixture was evaporated to dryness and the products were separated by flash column chromatography (eluting with $CHCl_3$) and analyzed by ^1H NMR spectroscopy. This procedure was repeated three times with the concentration of added dimethylphenylphosphine being varied; the amount of dimethylphenylphosphine, the reaction time, and the allylic alcohol product yields are listed below.

Added $PhP(Me)_2$ Equivalents/Cu	Reaction time (h)	Allylic alcohol yield (%)
4	24	60
6	3.0	60
12	20	21

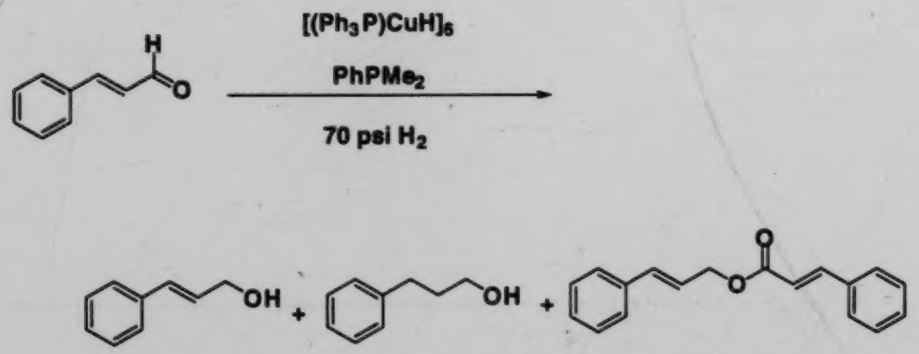
4. Hydrogen Pressure Effects:

General procedure A (for 70 psi pressure reactions). In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), benzene (0.4-0.8 M in substrate), dimethylphenylphosphine (0.013 g, 0.097 mmol), and *tert*-butanol (0.048 g, 0.65 mmol) were placed into a small vial. The organic substrate (0.32 mmol) was added and the resulting solution was transferred into a Fisher & Porter medium pressure vessel equipped with magnetic stirbar. The sealed vessel was removed from the glove box, connected to a hydrogen cylinder, flushed several times by pressurizing with H_2 and releasing the pressure, and then charged with H_2 to the indicated pressure (70 psi.). The reaction solution was stirred under 70 psi of H_2 until the reaction was complete by TLC analysis. The pressure was released and the vessel was opened to air. After stirring for several min, the resulting suspension was filtered though a pipette filled with cotton and celite, which was then washed with a little benzene. The solvent was evaporated *in vacuo* and the residue was taken up into C_6D_6 for ^1H NMR spectroscopic analysis.

General procedure B (for 500 psi pressure reactions): In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), benzene (0.4-0.8 M in substrate),

dimethylphenylphosphine (0.013 g, 0.097 mmol), and *tert*-butanol (0.048 g, 0.65 mmol) were placed into a small vial. The organic substrate (0.32 mmol) was then added and the resulting solution was transferred into a glass liner containing a magnetic stirbar, which was then sealed inside a stainless steel high pressure autoclave. The sealed vessel was removed from the glove box, connected to a hydrogen cylinder, flushed several times by pressurizing H_2 and releasing the pressure and then charged with H_2 to the indicated pressure (500 psi). The reaction solution was stirred under 500 psi pressure of H_2 for the designated time. The pressure was then released and the vessel was opened to air. After stirring for several min, the suspension was filtered though a pipette filled with cotton and celite and washed with a little benzene. The solvent was evaporated *in vacuo* and the residue was taken up into C_6D_6 for ^1H NMR spectroscopic analysis.

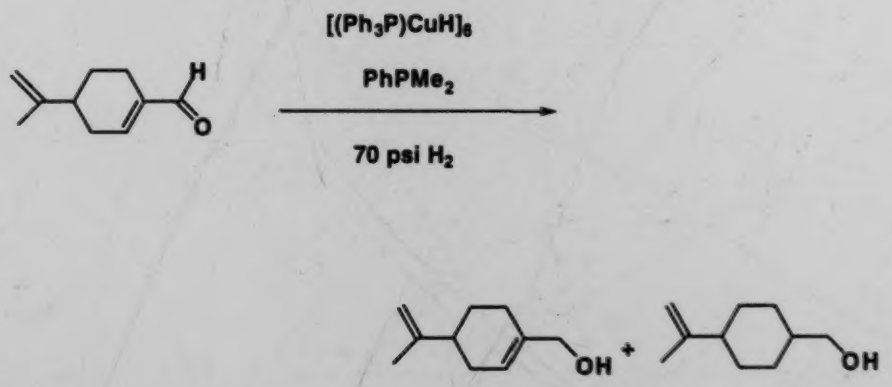
a. Reduction of *trans*-cinnamaldehyde under 70 psi of H_2.



Using the general procedure A, *trans*-cinnamaldehyde (0.043 g, 0.32 mmol) was hydrogenated under 70 psi pressure of hydrogen for 4 h. The crude ^1H NMR spectrum showed that the allylic alcohol and the saturated alcohol were formed in a ratio of 32 : 1 by ^1H NMR integration using a long pulse delay. The products were isolated via short

path silica gel flash chromatography (10 : 1 hexane/ethyl acetate), giving the inseparable allylic alcohol and saturated alcohol products (combined yield 0.041 g, 94%). The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of *trans*- cinnamaldehyde with $NaBH_4/CeCl_3$. The saturated alcohol product was identified by comparison to an authentic sample prepared by catalytic hydrogenation of the authentic allylic alcohol over Pd/C at 100 psi hydrogen pressure in ethyl acetate (*vide supra*). A third product (about 0.002 g) was also recovered, tentatively identified as the Tischenko reaction product $PhCH{=}CHCH_2OC(O)CH{=}CHPh$: partial ^1H NMR (200 MHz, C_6D_6) δ 4.75 (dd, J = 7.5, 1.5 Hz, 2 H), 6.20 (dt, J = 15.5, 7.5 Hz, 1 H), 6.49 (d, J = 15.5 Hz, 1 H), 6.68 (d, J = 15.5 Hz, 1 H), 6.9-7.3 (m, aromatic-H), 7.85 (d, J = 15.5 Hz, 1 H).

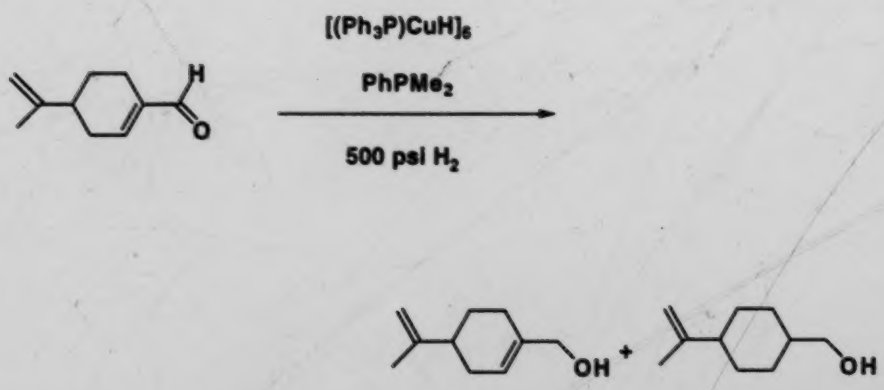
b. Reduction of perillaldehyde under 70 psi of H_2.



Using the general procedure A, perillaldehyde (0.049 g, 0.32 mmol) was hydrogenated under 70 psi pressure of hydrogen for 21h. The crude ^1H NMR spectrum showed 70% conversion, with the allylic alcohol and saturated alcohol formed in a ratio of

29 : 1. The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of perillaldehyde with $NaBH_4/CeCl_3$: ^1H NMR (360 MHz, C6D6) δ 1.41 m, 1 H), 1.65 (s, 3 H), 1.76 (m, 1 H), 1.85-2.12 (m, 5 H), 3.88 (br s, 2 H), 4.78 (s, 2 H), 5.61 (m, 1 H). The saturated alcohol product was identified by comparison to an authentic sample.[64] The reaction did not go to completion when the reaction time was increased to 48 h.

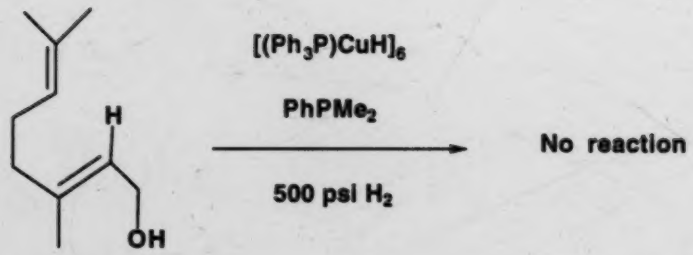
c. Reduction of perillaldehyde under 500 psi of H_2.



Using the general procedure B, perillaldehyde (0.049 g, 0.32 mmol) was hydrogenated under 500 psi pressure of hydrogen for 18 h. The crude ^1H NMR spectrum showed that the allylic alcohol and the saturated alcohol were formed in a ratio of 32 : 1. The products were isolated via short path silica gel flash chromatography (7 : 1 hexane/ethyl acetate), giving the inseparable allylic alcohol and saturated alcohol products (0.047 g, 95%). The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of perillaldehyde with $NaBH_4/CeCl_3$. The saturated alcohol product was identified by comparison to an authentic sample.[64]

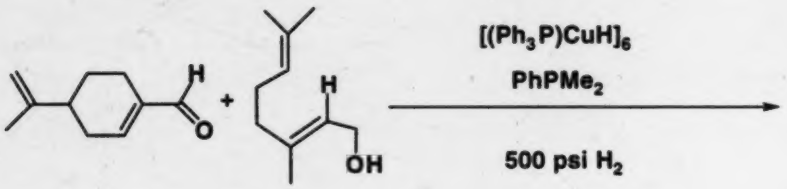
5. Allylic Alcohol Reduction Test

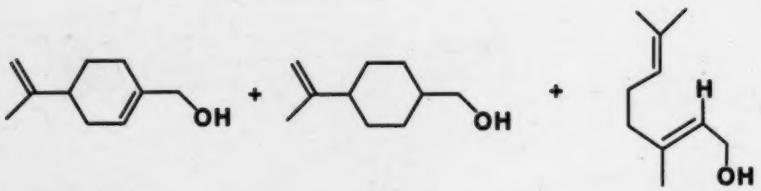
a. Reduction of geraniol under 500 psi of H_2.



Following the general procedure B, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), C_6D_6 (0.4-0.8 M in substrate), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) were placed into a small vial. Geraniol (0.050 g, 0.32 mmol) was added, and the mixture solution was hydrogenated under 500 psi pressure of hydrogen for 18 h. The crude ^1H NMR spectrum showed that none of the corresponding saturated alcohol was formed.

b. Reduction of perillaldehyde in the presence of geraniol (under 500 psi of H_2).





Following the general procedure B, two compounds, perillaldehyde (0.049 g, 0.32 mmol) and geraniol (0.050 g, 0.32 mmol) were hydrogenated under 500 psi pressure of hydrogen for 18h. The crude ^1H NMR spectrum showed that all of the perillaldehyde was reduced to corresponding allylic alcohol, with only trace of the corresponding saturated alcohol produced. No reduction of geraniol was observed. The compounds were identified by comparisons to authentic samples.

General procedure for the catalytic hydrogenation of α,β-unsaturated aldehydes and ketones using optimized reaction conditions (reaction conditions A, B, andC).

In the glove box, 0.0027 mmol $[(Ph_3P)CuH]_6$ (0.016 mmol Cu), C_6H_6 or THF (0.4-0.8 M in substrate), Me_2PPh (6 equiv/Cu), *tert* -butanol (40 equiv/Cu) were placed

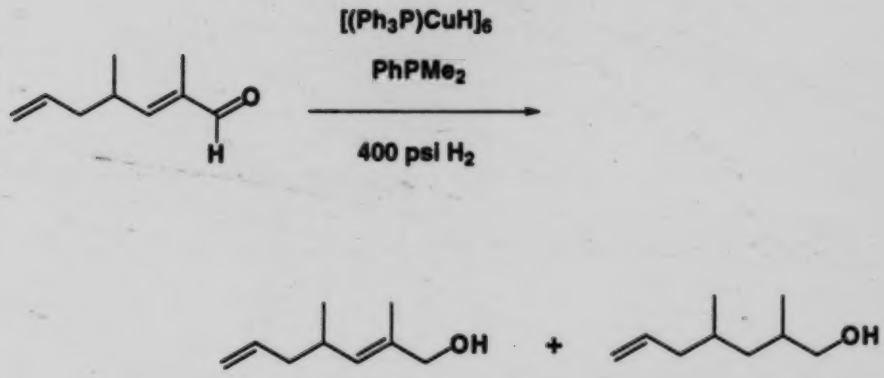
into a small vial. The substrate (10-40 equiv/Cu) was then added. The resulting mixture was transferred to a Fisher & Porter medium pressure vessel (for 70 psi reactions) equipped with magnetic stirbar (Conditions A) or to a glass liner containing a magnetic stirbar, which was then sealed inside a stainless steel high pressure autoclave for 400 psi reactions (Conditions B) or for 500 psi reactions (Conditions C). The sealed vessel was removed from the glove box, connected to a hydrogen cylinder, flushed several times by pressurizing with H_2 and releasing the pressure and then charged with H_2, up to the indicated pressure. Stirring was initiated after pressurization and upon completion of the reaction, the pressure was released and the vessel was opened to air. After stirring for several minutes, the resulting suspension was filtered though a pipette filled with cotton and celite and washed with a little reaction solvent. The solvent was evaporated *in vacuo* and the residue was taken up into C_6D_6 for ^1H NMR spectroscopic analysis. The ratio of allylic alcohol to saturated alcohol was determined by relative NMR integration at long pulse delay, after which the products were purified by short path silica gel flash chromatography .

Reaction conditions D. In the glove box, a glass–lined high-pressure autoclave containing a magnetic stir bar was charged with CuCl (0.016 mmol), NaO^tBu (0.016 mmol), C_6H_6 (0.6 mL), Me_2PPh (6 equiv/Cu), and *tert*-butanol (40 equiv/Cu). Substrate (20 equiv/Cu) was then added, and the other operations are as described above. The reaction was performed at 1000 psi pressure of hydrogen.

Identification of products. Products were identified by comparison with authentic materials prepared by unambiguous synthesis. Authentic allylic alcohols were prepared by the previously reported method using $CeCl_3$ and $NaBH_4$ in methanol or

ethanol.[61] Saturated alcohols were prepared by catalytic hydrogenation of the corresponding authentic allylic alcohols(H_2, Pd/C).[175] The saturated alcohol derived from the α,β–unsaturated aldehydes can also be prepared directly by a method developed in this group.[45] For example, citral (0.148 g, 0.974 mmol) was added to a mixture of $[(Ph_3P)CuH]_6$ (0.859 g, 0.438 mmol, 2.7 hydride equiv) in benzene (10-11 mL) and excess water (0.350 mL, 20 equiv) at room temperature under nitrogen. Complete reduction was effected over 32 h, after which the reaction mixture was exposed to air, stirred for several hours, and filtered through celite to give a light orange solution. Concentration and purification of the residue by flash column chromatography (9 : 1 hexanes/ethyl acetate) afforded citronellol (0.113 g, 74%).

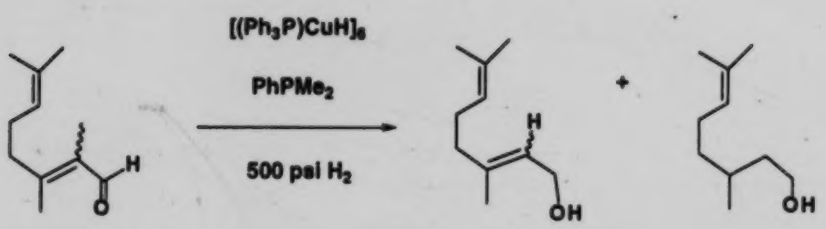
Reduction of 2,4-dimethyl-2,6-heptadienal (Conditions B).



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and 2,4-dimethyl-2,6-heptadienal (0.045 g, 0.32 mmol) were combined in C_6H_6 as described and stirred under 400 psi pressure of hydrogen for 30 h. After work-up, the crude ^1H NMR spectrum showed that the allylic alcohol and the saturated alcohol were formed in a ratio of 16 : 1.

The products were isolated via short path silica gel flash chromatography (3 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.042 g, 91%). The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of 2,4-dimethyl-2,6-heptadienal with $NaBH_4/CeCl_3$: ^1H NMR (360 MHz, C_6D_6) δ 0.91 (d, J = 7.5 Hz, 3 H), 1.52 (s, 3 H), 1.96 (t, J = 6.1 Hz, 2 H), 2.39 (m, 1 H), 3.80 (br s, 2 H), 4.91 (m, 2 H), 5.17 (d, J = 8Hz, 1 H), 5.75 (m, 1 H). The saturated alcohol product was identified by comparison to an authentic sample made previously in this group.[45]

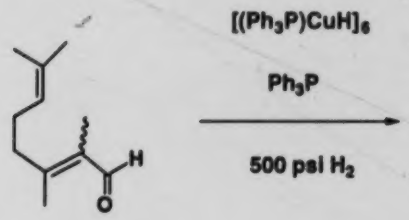
Reduction of citral (Conditions C).



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and citral (0.049 g, 0.32 mmol) were combined in C_6D_6 as described and stirred under 500 psi pressure of hydrogen for 15 h. After filtration, the crude ^1H NMR spectrum showed the presence of allylic alcohol and the saturated alcohol in a ratio of 11 : 1. The products were isolated after evaporation of the volatiles via short path silica gel flash chromatography (7 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.045 g, 90%). The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of citral with $NaBH_4/CeCl_3$: ^1H NMR (200 MHz, C_6D_6) δ 1.49 (br s, 6 H), 1.59 (br s, 3 H), 4.02 (d, J = 6.8 Hz, 2 H), 4.90-5.25 (m, 1 H). The

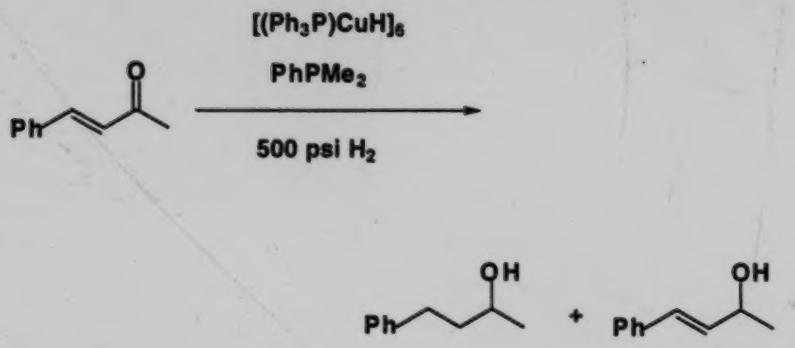
saturated alcohol product was identified by comparison to an authentic sample made previously in this group.[45]

Reduction of citral using $[(Ph_3P)CuH]_6$ and added triphenylphosphine, catalyst comparison.



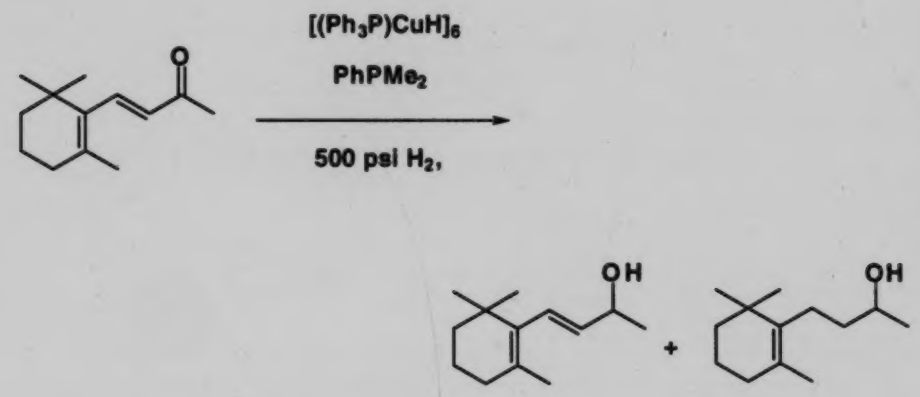
This procedure was identical to above reaction conditions except using 6 equivalents of triphenylphosphine instead of dimethylphenylphosphine. The reaction solution was hydrogenated under 500 psi pressure of hydrogen for 25 h. The resulting solution was homogeneous yellow. The crude ^1H NMR spectrum showed that most of the starting material was not consumed and only a trace amount of the allylic alcohol product was formed. No saturated aldehyde and alcohol products were found.

Reduction of *trans*-4-phenyl-3-buten-2-one (Conditions C).



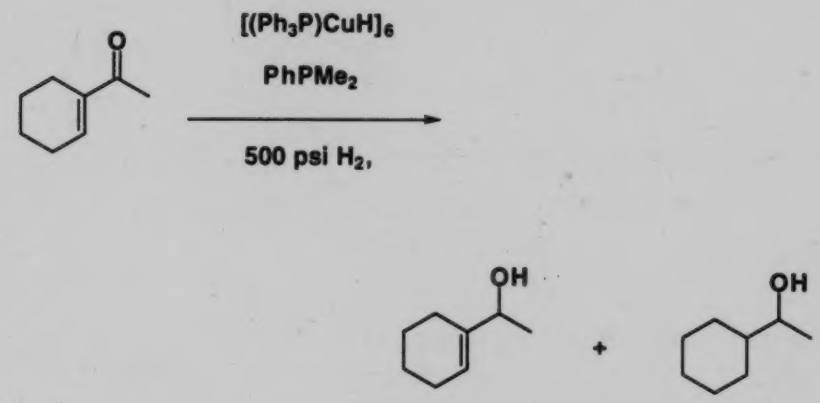
$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and *trans*-4-phenyl-3-buten-2-one (0.047 g, 0.32 mmol) were combined in benzene as described and stirred under 500 psi pressure of hydrogen for 18 h. After hydrogenation, acetic anhydride (0.5 mL) and pyridine (1 mL) were added to the crude mixture solution. The reaction solution was stirred at 0 °C for one h and then stirred at room temperature until all the product was acetylated by TLC analysis. The volatiles were evaporated *in vacuo* and the residue was purified by silica gel flash chromatography. The acetylated allylic alcohol and saturated alcohol products were obtained (0.051 g, 81%) in a ratio of 12 : 1. The acetylated allylic alcohol product was identified by comparison to an authentic sample, which was prepared by reduction of *trans*-4-phenyl-3-buten-2-one with $NaBH_4$ and $CeCl_3$, followed by acetylation of the reduction product using acetic anhydride and pyridine: ^{1}H NMR (300 MHz, C6D6) δ 1.21 (d, J =7.5 Hz, 3 H), 1.72 (s, 3H), 5.58 (m, 1 H), 6.08 (dd, J = 15.5, 7.5 Hz, 1 H), 6.51 (d, J = 15.5 Hz, 1 H), 6.95-7.25 (m, aromatic-H). The acetylated saturated alcohol product was identified by comparison to an authentic sample prepared by catalytic hydrogenation of the allylic alcohol over Pd/C, followed by acetylation of the hydrogenated product using acetic anhydride and pyridine: ^{1}H NMR (300 MHz, C_6D_6) δ 1.11 (d, J = 6.1Hz, 3 H), 1.79 (s, 3 H), 1.83 (s, 2 H), 2.45-2.70 (m, 2 H), 4.90-5.08 (m, 1 H), 7.02-7.38 (m, aromatic-H).

Reduction of β–ionone (Conditions C).



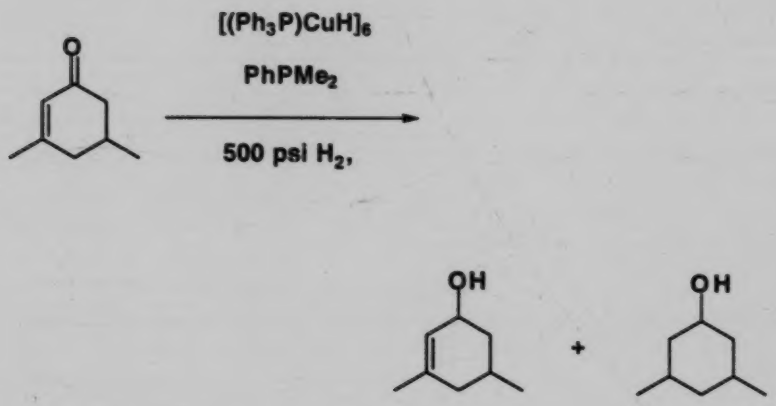
$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and β-ionone (0.062 g, 0.32 mmol) were combined in benzene as described and stirred under 500 psi pressure of hydrogen for 26 h. After work-up, the crude ^1H NMR spectrum showed the presence of the allylic alcohol and saturated alcohol products in a ratio of 49 : 1. The products were isolated via short path silica gel flash chromatography (10 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.056 g, 89%). The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of the substrate with $NaBH_4/CeCl_3$: ^1H NMR (300 MHz, C_6D_6) δ 1.02 (s, 6 H), 1.18 (d, J = 6.1 Hz, 3 H), 1.41 (m, 2 H), 1.52 (m, 2 H), 1.67 (s, 3 H), 1.90 (m, 2 H), 4.13 (m, 1 H), 5.47 (dd, J = 15.5, 6.2 Hz, 1 H), 6.03 (d, J = 15.5 Hz, 1 H). The saturated alcohol product was identified by comparison to an authentic sample.[176]

Reduction of 1-acetyl-1-cyclohexene (Conditions C).



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and 1-acetyl-1-cyclohexene (0.040 g, 0.32 mmol) were combined in benzene as described and stirred under 500 psi pressure of hydrogen for 20 h. After work-up, the crude ^1H NMR spectrum showed the presence of the allylic alcohol and saturated alcohol products in a ratio of 17 : 1. The products were isolated via short path silica gel flash chromatography (4 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.038 g, 94%). The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of 1-acetyl-1-cyclohexene with $NaBH_4/CeCl_3$: ^1H NMR (400 MHz, C_6D_6) δ 1.16 (d, J = 6.5 Hz, 3 H), 1.35-1.60 (m, 4 H), 1.75-2.05 (m, 4 H), 3.94 (quartet, J = 6.3 Hz, 1 H), 5.53 (br s, 1 H). The saturated alcohol product was identified by comparison to an authentic sample prepared by catalytic hydrogenation of the authentic allylic alcohol over Pd/C at one atmosphere hydrogen pressure in ethyl acetate. The characteristic ^1H NMR (400 MHz, C_6D_6) signal for the saturated alcohol used in product identification and ratio determination appears at δ 3.36 (quintet, J = 6.3 Hz, 1 H).

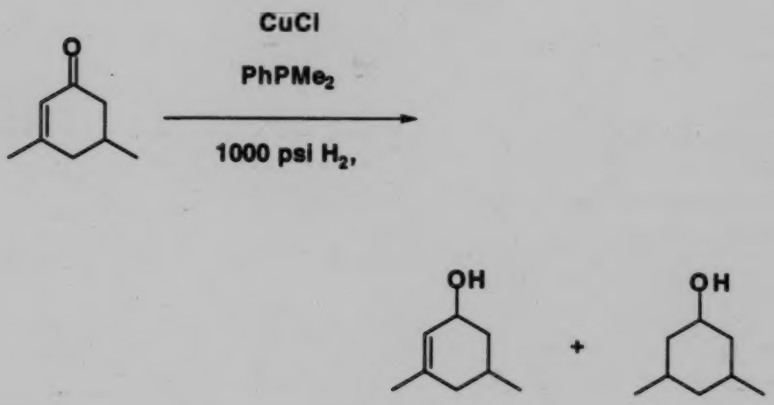
Reduction of 3,5-dimethylcyclohexenone (Conditions C).



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and 3,5-dimethylcyclohexenone (0.040 g, 0.32 mmol) were combined in benzene as described and stirred under 500 psi pressure of hydrogen for 20 h. After work-up, the crude ^1H NMR spectrum showed the presence of the allylic alcohol and saturated alcohol products in a ratio of 2.7 : 1. The allylic alcohol consists of two isomers, trans : cis = 92 : 8. The saturated alcohol also consists of two isomers, trans : cis = 29 : 71. The products were isolated via short path silica gel flash chromatography (3 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.036 g, 90%). The products were identified by comparison of their ^1H NMR spectra to that of commercially available standards or to that of authentic samples prepared by unambiguous means. The partial ^1H NMR (400 MHz, C_6D_6) signals used in product identification and ratio determination are as follows: allylic alcohol (2 isomers), major trans δ 5.45 (br s, 1 H), 4.19 (m, 1 H), 1.53 (s, 3 H), 0.81 (d, J = 6.4 Hz, 3 H). Minor cis δ 5.5 (m, 1 H), 4.10 (m, 1 H). Saturated alcohol (2

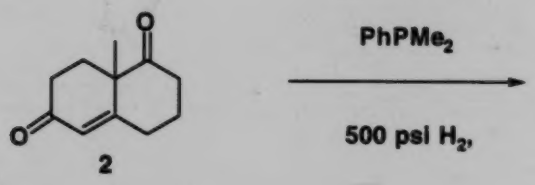
isomers), major trans OH δ 4.05 (apparent quintet tt, J = 2.9, 2.7 Hz, 1 H), 0.86 (d, J = 6.7 Hz, 3 H). Minor cis OH δ 3.57 (tt, J = 10.9, 4.2 Hz, 1 H), 0.74 (d, J = 6.6Hz, 6 H).

Reduction of 3,5-dimethyl cyclohexenone (Conditions D).



CuCl (1.6 mg, 0.016 mmol), NaO^{t}Bu (1.5 mg, 0.016 mmol), Me_2PPh (13.4 mg, 0.096 mmol), *tert*-butanol (48 mg, 0.65 mmol) and 3,5-dimethylcyclohexenone (0.040 g, 0.32 mmol) were combined in C_6H_6 (0.6 mL) as described in the general procedure and stirred at 1000 psi pressure of hydrogen for 24 h. After work-up, the crude ^{1}H NMR spectrum showed the presence of the allylic alcohol and saturated alcohol products in a ratio of 4.4 : 1. The products were isolated via short path silica gel flash chromatography (3 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.037 g, 92%). The products were identified by comparison of their ^{1}H NMR spectra to those of commercially available standards or to those of authentic samples prepared by unambiguous means. The partial ^{1}H NMR (400 MHz, C_6D_6) data used in product identification and ratio determination are the same as the data in the above experiment.

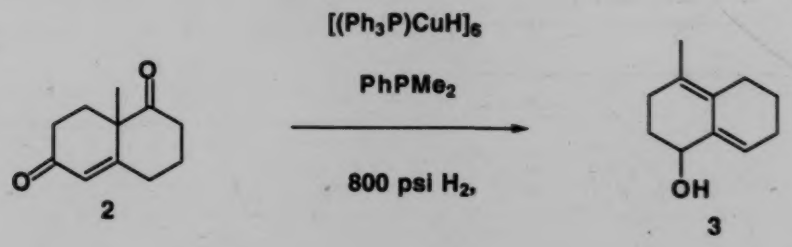
Reduction of Wieland-Miescher ketone under 500 psi of H_2.



2

In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), C_6D_6 (0.4-0.8 M in substrate), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) were placed into a small vial. Wieland-Miescher ketone (0.058 g, 0.32 mmol) was then added. The solution was transferred into a glass liner containing a magnetic stirbar, which was then sealed inside a stainless steel high pressure autoclave. The sealed vessel was transported out of the glove box, connected to a hydrogen cylinder, flushed several times by pressurizing and releasing H_2, and charged with H_2 to the indicated pressure (500 psi.). After stirring for 24 h, the pressure was released and the vessel was opened to air. The resulting solution was purple with some shiny copper mirror found on the surface of the glass liner. After stirring under air for several minutes, the resulting suspension was filtered though a pipette filled with cotton and celite. The crude ^1H NMR spectrum and TLC showed that the reaction solution contained more than four different products which were difficult to identify. When the reaction was performed under identical conditions except using THF as a solvent, the reaction still yielded a complicated mixture.

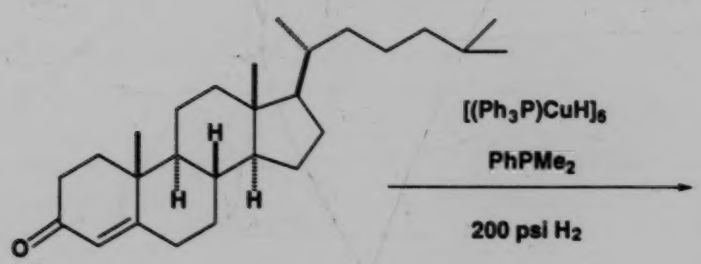
Reduction of Wieland-Miescher ketone under 800 psi of H_2.



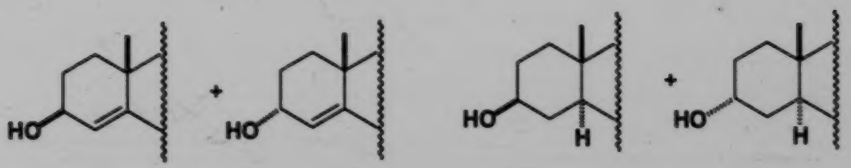
2 3

This reaction was performed under conditions identical to above procedure, except that the hydrogen pressure was increased to 800 psi. The reaction solution was stirred under 800 psi pressure of hydrogen for 22 h. Upon completion, the pressure was released and the vessel was opened to air. The resulting solution was brown–black with some copper mirror formed on the surface of the glass liner. After stirring for several minutes, the resulting suspension was filtered though a pipette filled with cotton and celite. The filtrate was concentrated and the residue was separated by short path silica gel flash chromatography (4 : 1 hexane/ethyl acetate) giving a white solid, 4-methyl-1,2,3,5,6,7-hexahydro-naphthalen-1-ol **5** (43.5 mg, 82%). The structure assignment of **5** was based on the analysis of the spectroscopic data: FTIR (KCl) 3100–3600 (br s), 2924 (s), 1644 (m), 1372 (m), 1357 (w), 1340 (w), 1163 (w), 1093 (s), 1020 (w), 925 (w), 878 (w), 865 (w), 801 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (t, J = 4.0 Hz, 1 H), 4.19 (t, J = 3.6 Hz, 1 H), 2.30 (m, 3 H), 2.15 (m, 3 H), 1.80 (m, 2 H), 1.70 (m, 6 H); ^{13}C $\{^1H\}$ NMR (75 MHz, CDCl3, APT) δ 137.5, 128.2, 125.4, 122.8, 70.2, 30.5, 28.6, 26.1, 25.5, 22.8, 19.0; INAPT (75 MHz, C_6D_6) irridiate proton at δ = 5.71 $\leftrightarrow$ δ 125.4, 70.1, 25.5, 22.8; irridiate proton at δ = 4.19 $\leftrightarrow$ δ 137.4, 125.4, 122.8, 30.4, 28.6; HMQC (300 MHz, $CDCl_3$, selected data only) δ 122.8 $\leftrightarrow$ δ 5.71; δ 70.2 $\leftrightarrow$ δ 4.19; HMBC (300 MHz, $CDCl_3$, selected data only) δ 4.19 $\leftrightarrow$ δ 137.4, 125.4, 122.8, 28.6; δ 5.71 $\leftrightarrow$ δ 125.4, 70.1, 25.5, 22.8; HRMS calcd. *m/z* for $C_{11}H_{16}O$ 164.12012, found 164.12120.

Reduction of 4-cholesten-3-one under 200 psi of H_2.



12



13 14 15 16

In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), dimethylphenylphosphine (0.013 g, 0.097 mmol), *tert*-butanol (0.5 mL), and benzene (0.5 mL) were placed into a small vial. 4-cholesten-3-one (0.062 g, 0.16 mmol) was then added into the vial. This reaction uses more *tert*-butanol because 4-cholesten-3-one has low solubility in benzene, but good solubility in *tert*-butanol. The resulting solution was transferred into a glass liner containing a magnetic stirbar, which was then sealed inside a stainless steel high pressure autoclave. The sealed vessel was transported out of the glove box, connected to a hydrogen cylinder, flushed several times by pressurizing and releasing H_2, and finally charged with H_2 to the indicated pressure (200 psi.). After stirring for 22 h, the pressure was released and the vessel was opened to air. The reaction solution was stirred for several more minutes, and then filtered though a pipette filled with cotton and

celite. The solvent of the filtrate was evaporated *in vacuo* and the residue was taken up into C_6D_6 for ^1H NMR spectroscopic analysis. The crude ^1H NMR spectrum showed the presence of two allylic alcohols **12** and **13** (91%) and two saturated alcohols **14** and **15** (9%). The two allylic alcohols were formed in a ratio of 6 : 1, the major product **12** (3β-OH) and the minor product **13** (3α-OH). The two saturated alcohos were formed in a ratio of 5 : 1, the major product **14 trans** (3β-OH) and minor product **15 trans** (3α-OH). The products were identified individually by analysis and comparison of the spectroscopic data to that of authentic samples.[43,67,68] The product ratios are measured in the crude reaction mixture by integration of the signals for the 3-methine protons in the ^1H NMR spectrum (400 MHz, $CDCl_3$). For the allylic alcohols, the 3-methine protons appear at δ 4.15 (m, 1 H, major **12** 3β-OH), and δ 4.07 (bs, 1 H, minor **13** 3α-OH). The olefin proton of the allylic alcohol products appear at δ 5.28 (bs, 1 H, major **12** 3β-OH) and δ 5.46 (d, J = 5.0 Hz, 1 H, minor **13** 3α–OH). For the two saturated alcohos, the 3-methine protons appear at δ 3.58 (tt, J = 4.9, 11.0 Hz, 1 H, major **14 trans** 3β–OH), and δ 4.03 (m, 1 H, minor **15 trans** 3α–OH). When pyridine-d_5 was used as ^1H NMR solvent, integration of the spectrum gave identical results. The products were isolated via silica gel flash chromatography (eluent, chloroform) giving the inseparable allylic alcohol and saturated alcohol products (0.059 g, 95%).

Reduction of 4-cholesten-3-one under 500 psi of H_2.

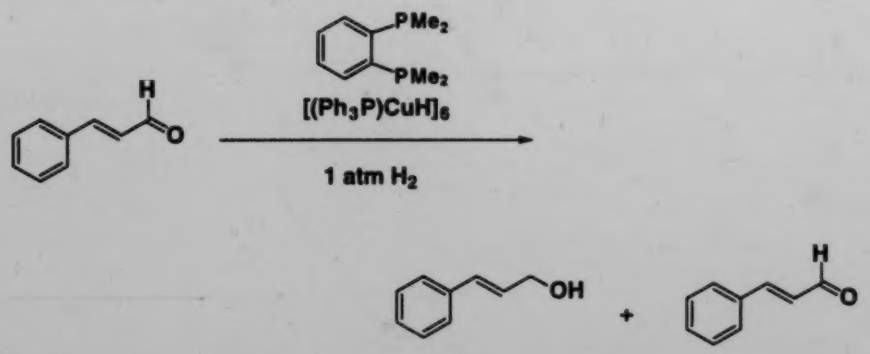
This reaction was identical to the above procedure, except the hydrogen pressure was increased to 500 psi. The reaction solution was stirred under 500 psi pressure of hydrogen for 22h. After work-up, the crude ^1H NMR spectrum showed the same products and stereochemical ratios as that of the above reaction. The isolated yield was 99%.

B. Investigation of the Chemoselectivity and Catalytic Activity of New Catalysts. Catalytic reduction of α,β–unsaturated ketones and aldehydes using $[(Ph_3P)CuH]_6$ with other added tertiary phosphine.

1. Bidendate phosphine derived catalysts

a. 1,2-bis(dimethylphosphino)benzene.

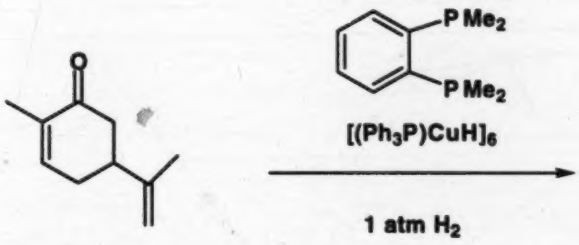
One atmosphere reduction of *trans*-cinnamaldehyde.



In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), benzene (0.4-0.8 M in substrate), 1,2-bis(dimethylphosphino)benzene (0.0064 g, 0.032 mmol), and *tert*-butanol (0.048 g, 0.65 mmol) were placed into a small vial. *Trans*-cinnamaldehyde (0.043 g, 0.32 mmol) was then added and the reaction solution transferred into a 25 mL Schlenk flask containing a magnetic stirbar. An additional 0.2 mL benzene was added to the vial to rinse any remaining material into the Schlenk flask. The flask was capped, removed from the glovebox, and filled with one atm of hydrogen after

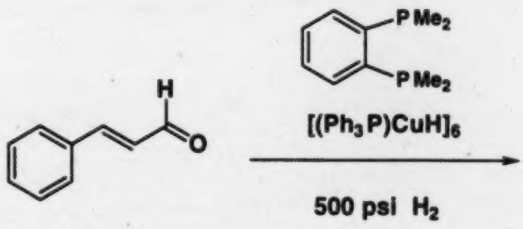
one "freeze-pump-thaw" degassing cycle. The solution was stirred under H_2 at room temperature for 8 h and then the reaction solution was exposed to air, work–up as described for other reduction reactions. Analysis of the crude mixture by ^1H NMR spectroscopy showed that the starting material and the corresponding allylic alcohol product were formed in a ratio of 10 : 1; no saturated alcohol product was observed. The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of *trans*-cinnamaldehyde with $NaBH_4/CeCl_3$. The saturated alcohol product was checked by comparison to an authentic sample prepared by catalytic hydrogenation of the authentic allylic alcohol over Pd/C at 100 psi hydrogen pressure in ethyl acetate (*vide supra*).

One atmosphere reduction of R-(-)carvone.



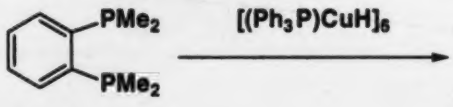
Identical to the above procedure, R-(-)-carvone (0.049 g, 0.32 mmol) was hydrogenated under one atmosphere pressure of hydrogen for 3 days. The crude ^1H NMR spectrum showed the presence of starting material and a mixture of unknown byproducts. No allylic alcohol or saturated alcohol product was observed.

Reduction of *trans*-cinnamaldehyde under 500 psi of H_2.



In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu) and benzene (0.4-0.8 M in substrate) were mixed in a small vial, resulting in the formation of a red solution. 1,2-Bis(dimethylphosphino)benzene (0.0064 g, 0.032 mmol) was added, and the solution color changed instantly from red to orange–yellow. The solution was treated with a solution of *tert*-butanol (0.048 g, 0.65 mmol) and *trans*-cinnamaldehyde (0.043 g, 0.32 mmol) in benzene, after which the solution color changed back to red. The combined solution was hydrogenated in a stainless steel autoclave under 500 psi pressure of hydrogen for 44 h. The pressure was released and the solution was opened to the air. After stirring for several minutes, The black suspension was filtered though a pipette filled with cotton and celite and washed with a little benzene. The solvent was evaporated *in vacuo* and the residue was taken up into C_6D_6 for ^1H NMR spectroscopic analysis. The crude ^1H NMR spectrum showed the presence of starting material and allylic alcohol in a ratio of 1.7 : 1; only a trace amount of the saturated alcohol was found.

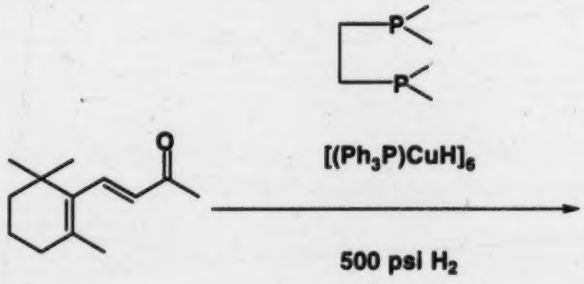
Catalyst investigation.



In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol), benzene-d_6 (0.8 mL), and 1,2-bis(dimethylphosphino)benzene (0.0064 g, 0.016 mmol) were mixed in a small vial. The resulting orange yellow solution was transferred into a NMR tube and the tube was sealed for ^1H NMR spectroscopic analysis. The ^1H NMR spectrum showed that the hydride signal in $[(Ph_3P)CuH]_6$ (δ = 3.52, br septet) had disappeared and a new broad singlet at high field (δ = 1.25, br s) appeared. The new broad singlet was partially obscured by other signals.

b. 1,2-bis(dimethylphosphino)ethane.

Reduction of β-ionone with 6 and 3 equivalents of 1,2-bis(dimethylphosphino)ethane. (Conditions C).



In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), benzene-d_6 (0.4-0.8 M in substrate), and 1,2-bis(dimethylphosphine)ethane (0.014 g, 0.097 mmol) were mixed in a small vial, resulting in the formation of an orange–yellow solution. The orange–yellow solution was treated with a solution of *tert*-butanol (0.048 g, 0.65 mmol)

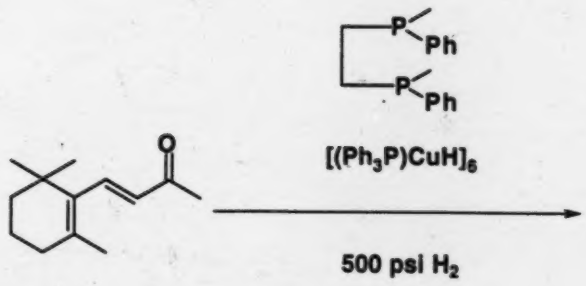
and β-ionone (0.062 g, 0.32 mmol) in benzene-d_6 (0.2 mL). The resulting solution was stirred under 500 psi pressure of hydrogen for 23 h. After work-up, the crude ^{1}H NMR spectrum showed that the starting material was predominant and only a trace amount of allylic alcohol product was formed. No saturated alcohol product was observed. The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of the substrate with $NaBH_4/CeCl_3$; the saturated alcohol product was checked by comparison to an authentic sample.[176] Under similar conditions, except using three equiv of 1,2-bis(dimethylphosphino)ethane, the reaction gave essentially the same results.

Reduction of β–ionone with one equivalent of 1,2-bis(dimethylphosphino)ethane.

Identical to the above procedure, except using 1 equiv 1,2-bis(dimehtylphosphine)ethane (0.0024 g, 0.016 mmol). The reaction solution was stirred under 500 psi pressure of hydrogen for 20 h. The crude ^{1}H NMR spectrum showed the presence of the starting material and the allylic alcohol in a ratio of 1.5 : 1; no saturated alcohol was observed.

c. 1,2-Bis(phenylmethylphosphino)ethane.

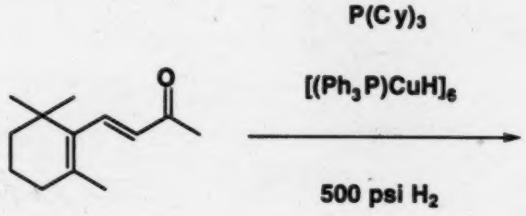
Reduction of β – ionone with 2 equivalents of 1,2-bis(phenylmethylphosphino)ethane.



Following the general procedure (**Conditions C**), 1,2-bis(phenylmethylphosphine)ethane (0.0088 g, 0.032 mmol),[69,70] $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), benzene-d_6 (0.8 mL), *tert*-butanol (0.048 g, 0.65 mmol), and β-ionone (0.062 g, 0.32 mmol) were mixed as previously described. The resulting solution was stirred under 500 psi pressure of hydrogen for 24 h. The crude ^{1}H NMR spectrum showed that no allylic alcohol or saturated alcohol product was formed.

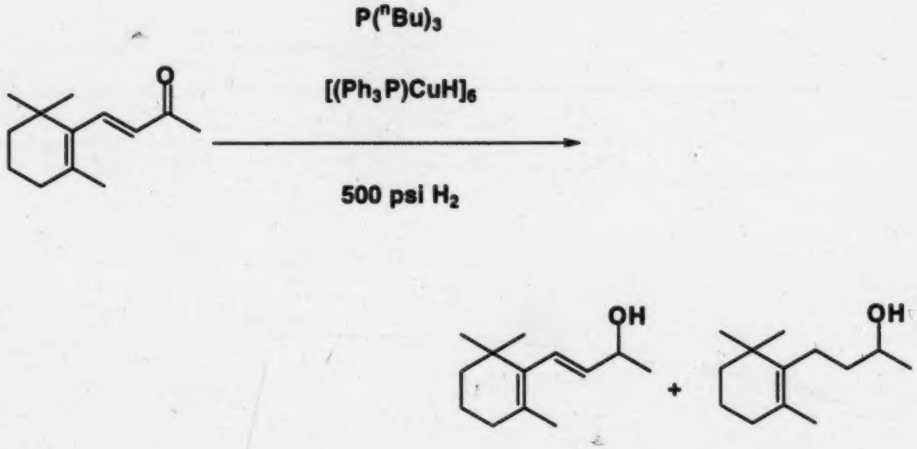
2. Common tertiary phosphine derived catalysts

Reduction of β–ionone with tricyclohexylphosphine.



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), tricyclohexylphosphine (0.027 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and β-ionone (0.062 g, 0.32 mmol) were combined in benzene-d_6 as previously described. Upon addition of the tricyclohexylphosphine to $[(Ph_3P)CuH]_6$ in benzene-d_6 (0.8 mL), the solution color changed from red to yellow. The resulting yellow solution was stirred under 500 psi pressure of hydrogen for 20 h. After work–up, the ^1H NMR spectrum of the crude product showed the presence of the starting material and saturated alcohol in a ration of 19 : 1; only trace of the allylic alcohol product (< 1%) was observed.

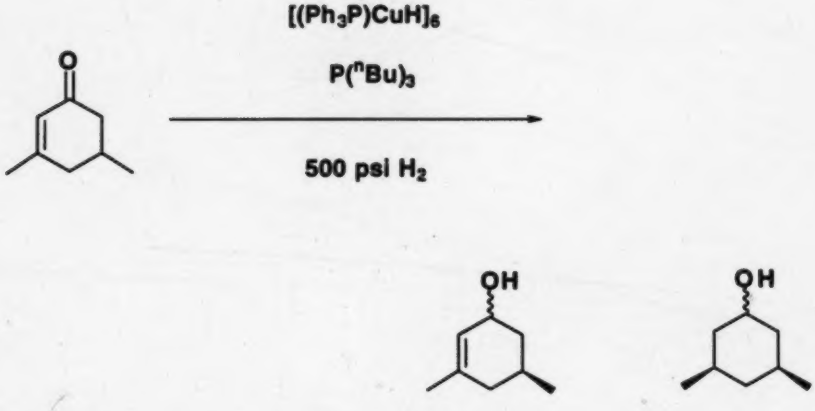
Reduction of β–ionone with tri-n-butylphosphine.



Following the general procedure (Conditions C), $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), tri-n-butylphosphine (0.019 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and β-ionone (0.062 g, 0.32 mmol) were combined in benzene-d_6 as described. When the tri-n-butylphosphine was mixed with $[(Ph_3P)CuH]_6$ in benzene-d_6 (0.8 mL), the solution color did not change from the initial red color. The reaction solution was

stirred under 500 psi pressure of hydrogen for 18 h, resulting in the formation of a homogeneous yellow solution. After work–up, the crude ^1H NMR spectrum showed complete conversion. The allylic alcohol and the saturated alcohol products were formed in a ratio of 3.7 : 1. The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of the substrate with $NaBH_4/CeCl_3$; the saturated alcohol product was checked by comparison to an authentic sample.

Reduction of 3,5-dimethylcyclohexenone with tri-n-butylphosphine.



Identical to the above procedure, 3,5-dimethyl cyclohexenone (0.040 g, 0.32 mmol) was hydrogenated under 500 psi pressure of hydrogen for 18 h. The crude ^1H NMR spectrum again showed complete conversion. The corresponding allylic alcohol and saturated alcohol products were formed in a ratio of 1 : 5. The allylic alcohol consisted of two isomers, trans OH : cis OH = 75 : 25. The saturated alcohol also consisted of two isomers, trans OH : cis OH = 53 : 47. The products were isolated via short path silica gel flash chromatography (3 : 1 hexane/ethyl acetate), giving the inseparable allylic alcohol and saturated alcohol products (0.034 g, 85%). The alcohol

products were identified by comparison of their ^1H NMR spectra to that of commercially available standards or to that of authentic samples prepared by unambiguous means. The partial ^1H NMR (400 MHz, C_6D_6) signals used in product identification and ratio determination are as follows: allylic alcohol (2 isomers), major trans δ 5.45 (br s, 1 H), 4.19 (m, 1 H), 1.53 (s, 3 H), 0.81 (d, J = 6.4 Hz, 3 H). Minor cis δ 5.5 (m, 1 H), 4.10 (m, 1 H). Saturated alcohol (2 isomers), major trans OH δ 4.05 (apparent quintet tt, J = 2.9, 2.7 Hz, 1 H), 0.86 (d, J = 6.7 Hz, 3 H); minor cis OH δ 3.57 (tt, J =10.9, 4.2 Hz, 1 H), 0.74 (d, J = 6.6Hz, 6 H).

Reduction of 3,5-dimethylcyclohexenone with triisopropylphosphine and trimethoxylphosphine.

Using the above procedure, except triisopropylphosphine or trimethoxylphosphine were used as the added phosphine. In either case, no reduction reaction was observed and only starting material was recovered after work–up and isolation.

3. Phenyl–substituted cyclic phosphine derived catalysts

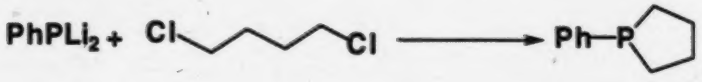
a. Synthesis of 1-phenylphospholane

Synthesis of dilithiophenylphosphine.

$$PhPCl_2 \longrightarrow PhPLi_2$$

In a 100 mL round bottom flask under nitrogen was added dry THF (20mL) and small pieces of lithium metal (0.3 g, 42 mmol, freshly cut). Phenylphosphine dichloride (1.8 g, 10 mmol) was added and the resulting solution was heated to reflux for 12 h. The red solution was transferred to a three neck flask via a pipet and the unreacted lithium metal was recovered. The red solution was directly used in the next reaction.

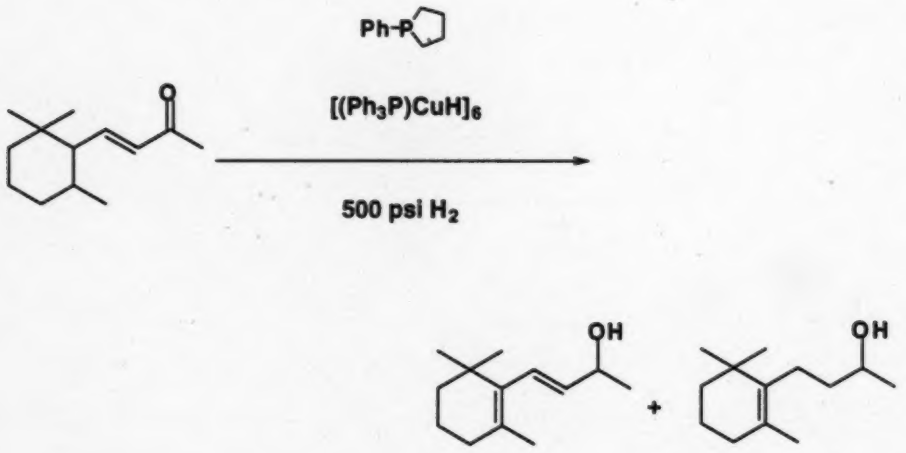
Synthesis of 1-phenylphospholane



To the red solution of $PhPLi_2$ in THF under nitrogen was added dropwise a solution of 1,4-dichlorobutane (1.27 g, 10 mmol) in THF (10 mL). The resulting mixture was heated to reflux for 2 h, during which time the solution color changed gradually from red to yellow and then to white. An unknow black substance appeared on the top of the solution. After cooling to room temperature, the solution was filtered through a pad of celite. The filtrate was concentrated and the residue was distilled under nitrogen. The product was collected at 3 torr/97-100 °C. Further purification was accomplished by using a inert atmosphere flash column chromatography eluting with hexanes. Yield: 168 mg, 10%. The product was spectroscopically identical to the reported compound.[76]

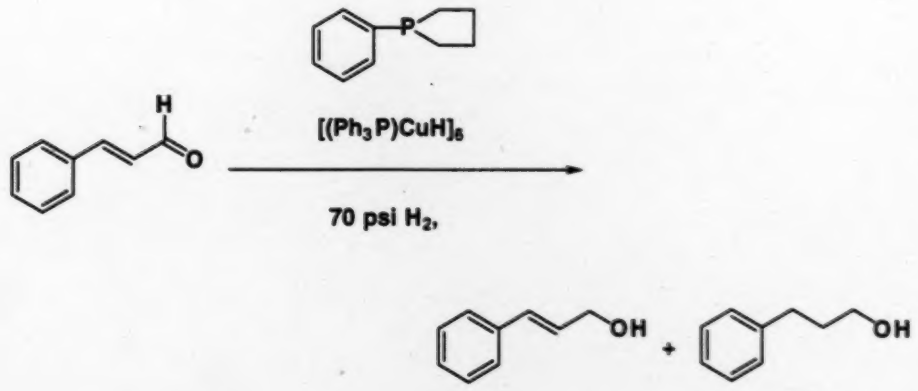
b. Reduction of α,β–unsaturated carbonyl compounds with added 1-phenylphospholane

Reduction of β–ionone with added 1-phenylphospholane.



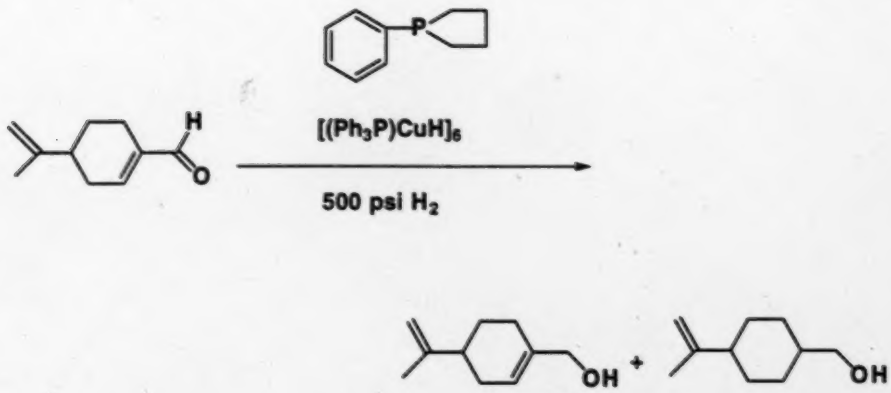
$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), 1-phenylphospholane (0.016 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and β-ionone (0.062 g, 0.32 mmol) were combined in benzene-d_6 as described in the general procedure. The reaction solution was stirred under 500 psi pressure of hydrogen for 21 h. After work–up, the crude ^1H NMR spectrum showed complete conversion, with the corresponding allylic alcohol and saturated alcohol products formed in a ration of 19 : 1. The products were isolated via short path silica gel flash chromatography (10 : 1 hexane/ethyl acetate), giving the inseparable allylic alcohol and saturated alcohol products (0.053 g, 84%).

Reduction of *trans*-cinnamaldehyde with added 1-phenylphospholane.



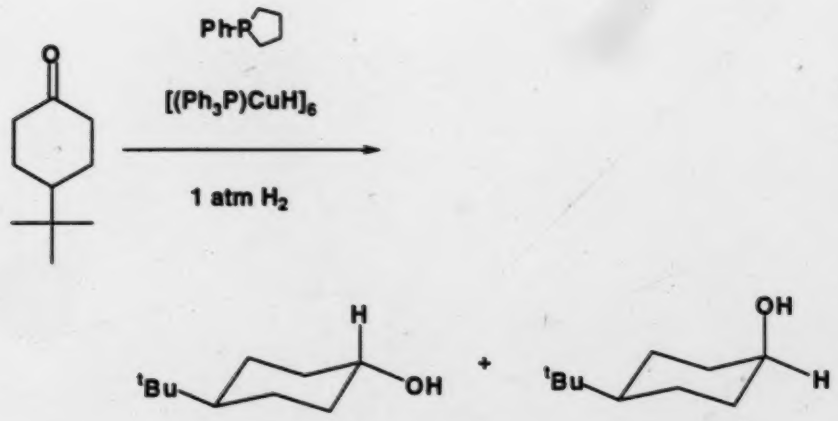
$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), 1-phenylphospholane (0.016 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and *trans*-cinnamaldehyde (0.043 g, 0.32 mmol) were combined in benzene-d_6 as described in the general procedure (Conditions C). The reaction solution was stirred under 500 psi pressure of hydrogen for 18 h. After work–up, the crude ^1H NMR spectrum showed complete conversion, with the corresponding allylic alcohol and saturated alcohol products formed in a ratio of 84 : 1. The products were isolated via short path silica gel flash chromatography (10 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.038 g, 89%).

Reduction of perillaldehyde with added 1-phenylphospholane.



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), 1-phenylphospholane (0.016 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and perillaldehyd (0.049 g, 0.32 mmol) were combined in benzene-d_6 (0.8 mL) as described in the general procedure (Conditions C). The reaction solution was stirred under 500 psi pressure of hydrogen for 18 h. After work–up, the crude ^1H NMR spectrum showed complete conversion. The corresponding allylic alcohol and saturated alcohol products were formed in a ratio of 38 : 1. The products were isolated via short path silica gel flash chromatography (10 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.041 g, 83%). The allylic alcohol product was identified by comparison to an authentic sample prepared by reduction of perillaldehyde with $NaBH_4/CeCl_3$ (*vida supra*). The saturated alcohol product was identified by comparison to an authentic sample.[64]

Reduction of 4-*tert*-butylcyclohexanone with added 1-phenylphospholane (under one atomsphere pressure of hydrogen).

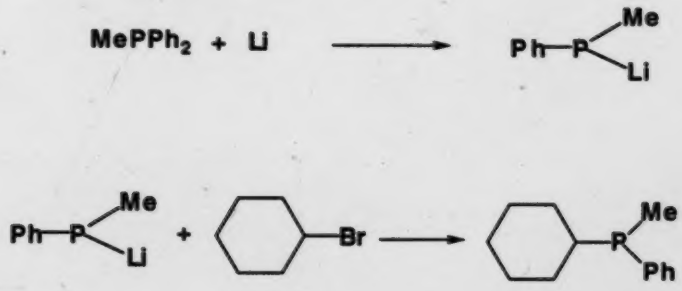


In the glove box, $[(Ph_3P)CuH]_6$ (0.026 g, 0.0135 mmol, 5 mol% Cu), benzene (0.5 mL), and 1-phenylphospholane (0.016 g, 0.097 mmol) were placed into a small vial. *tert*-Butanol (0.048 g, 0.65 mmol), benzene (0.6 mL) and 4-*tert*-butylcyclohexanone (0.049 g, 0.32 mmol) were placed in another small vial and the vial was capped with septum. The catalyst mixture was transferred into a 25 mL Schlenk flask containing a magnetic stirbar and an additional 0.2 mL of benzene was added to the vial to rinse any remaining material into the Schlenk flask. The flask was capped, removed from the glovebox, and filled with one atm of hydrogen after one "freeze-pump-thaw" degassing cycle. The benzene solution of substrate and *tert*-butanol was transferred into this flask via cannula. The resulting solution was stirred under H_2 at room temperature for 24 h. After work–up as described, the crude ^1H NMR spectrum showed that all the starting material was consumed, and *trans*-4-*tert*-butylcyclohexan-1-ol and *cis*-4-*tert*-butylcyclohexan-1-ol were formed in a ratio of 2.5 : 1. The products were isolated via short path silica gel flash chromatography (6 : 1 pentane/ether) giving the inseparable *trans*-4-*tert*-butylcyclohexan-

1-ol and *cis*-4-*tert*-butylcyclohexan-1-ol products (0.046 g, 92%). The alcohol products were identified by comparison to an authentic sample.[43]

4. Racemic phenylmethylalkylphosphine

a. Synthesis of cyclohexylmethylphenylphosphine.

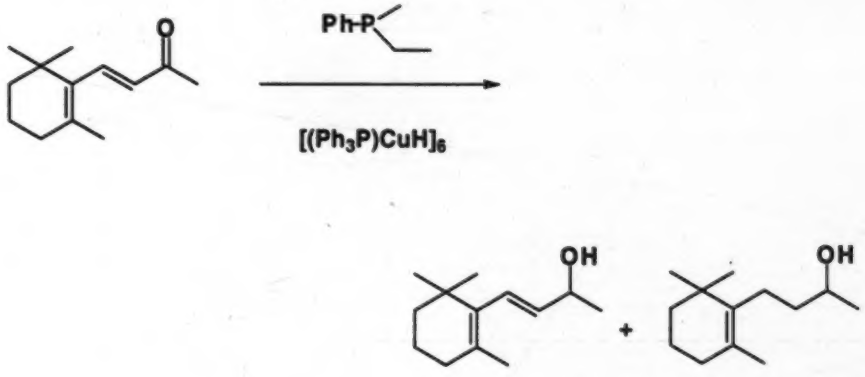


To a solution of diphenylmethylphosphine (3 g, 0.015 mol) in dry THF (30 mL) under nitrogen was added lithium metal in small pieces (0.25 g, 0.035 mol, freshly cut). The resulting solution was stirred for 5 h, after which the solution was cooled in ice-water bath and treated with a solution of cyclohexyl bromide (5 g, 0.03 mol) in dry THF (5 mL). The resulting solution was allowed to warm slowly to room temperature. After stirring at room temperature for one h, the reaction was quenched by the addition of water (20 mL, degassed) at low temperature (0 °C). When the hydrolysis was complete, the organic layer was removed and the aqueous layer was extracted several times with ether. The THF and ether extracts were combined and dried over sodium sulfate. After filtration, the filtrate was concentrated and the residue was distilled under vacuum. The product was collected at 135 °C/5 torr (1.5 g, 50%). Further purification was

accomplished by inert atmosphere flash column chromatography eluting with hexanes (*vide supra*). After the column separation, the product was redistilled to afford pure product. The spectroscopic data of the product was identical to that of the reported compound, which was synthesized by an alternative route.[82]

b. Reduction with added racemic phenylmethylalkyl phosphine

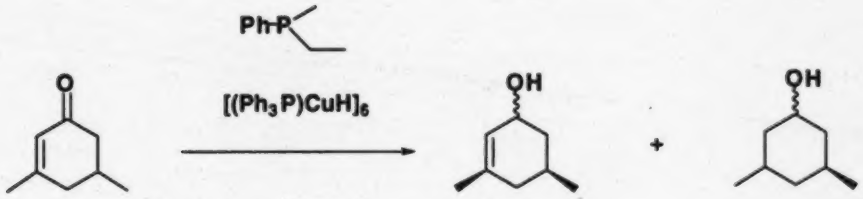
Reduction of β–ionone with added ethylmethylphenylphosphine.



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), ethylmethylphenylphosphine (0.015 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol), and β-ionone (0.062 g, 0.32 mmol) were combined in benzene-d_6 as described in the general procedure (Conditions C). The reaction solution was stirred under 500 psi pressure of hydrogen for 21 h. after work–up, the crude ^1H NMR spectrum showed that all the starting material was consumed and the corresponding allylic alcohol and saturated alcohol products were formed in a ratio of more than 50 : 1. The products were isolated

via short path silica gel flash chromatography (10 : 1 hexane/ethyl acetate) giving the inseparable allylic and saturated alcohols (0.060 g, 95%).

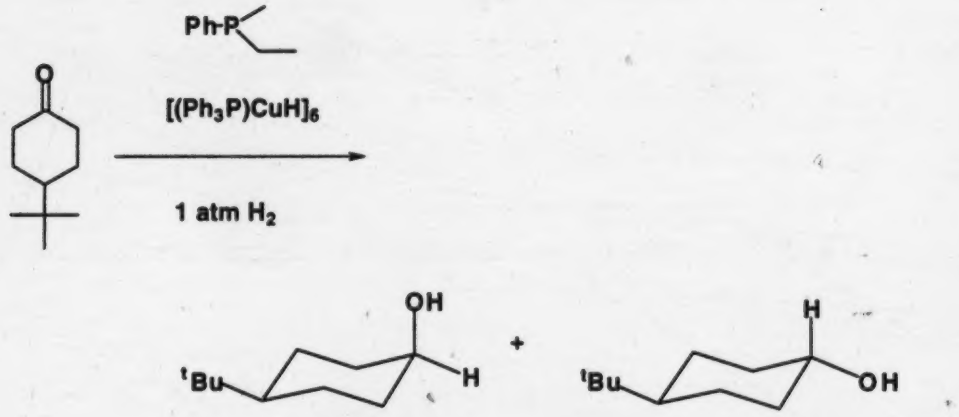
Reduction of 3,5-dimethylcyclohexenone with added ethylmethylphenylphosphine.



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), ethylmethylphenylphosphine (0.015 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol) and 3,5-dimethylcyclohexenone (0.040 g, 0.32 mmol) were combined in benzene as described in the general procedure (Conditions C). The resulting solution was stirred under 500 psi pressure of hydrogen for 20 h. After work–up, the crude ^1H NMR spectrum showed that the reaction was complete, and the corresponding allylic alcohol and saturated alcohol products were formed in a ratio of 3 : 1. The allylic alcohol consists of two isomers: trans OH : cis OH = 88 : 12; the saturated alcohol also consits of two isomers: trans OH : cis OH = 42 : 58. The products were isolated via short path silica gel flash chromatography (3 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.036 g, 90%). The alcohols were identified by comparison of their ^1H NMR spectra to those of commercially available standards or to authentic samples prepared by unambiguous means. The ^1H NMR (400 MHz, C_6D_6) signals used in product identification and ratio determination are as follows: allylic alcohol (2 isomers), major trans δ 5.45 (br s, 1 H), 4.19 (m, 1 H), 1.53 (s, 3 H), 0.81 (d, J = 6.4 Hz, 3 H), minor cis δ 5.5 (m, 1 H), 4.10 (m, 1 H). Saturated alcohol (2 isomers), trans OH δ

4.05 (apparent quintet:tt, J = 2.9, 2.7 Hz, 1 H), 0.86 (d, J = 6.7 Hz, 3 H), cis OH δ 3.57 (tt, J = 10.9, 4.2 Hz, 1 H), 0.74 (d, J = 6.6 Hz, 6 H).

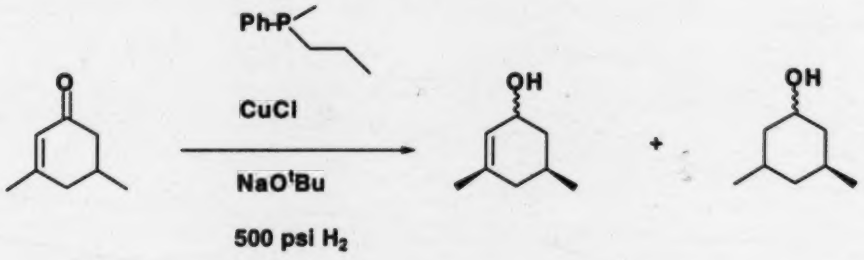
Reduction of 4-*tert*-butylcyclohexanone with added ethylmethylphenylphosphine under one atomsphere pressure of hydrogen.



In the glove box, $[(Ph_3P)CuH]_6$ (0.026 g, 0.0135 mmol, 5 mol% Cu), benzene (0.5 mL), and ethylmethylphenylphosphine (0.015 g, 0.097 mmol) were placed into a small vial. *Tert*-butanol (0.048 g, 0.65 mmol), benzene (0.6 mL), and 4-*tert*-butylcyclohexanone (0.049 g, 0.32 mmol) were added into another small vial and capped with a rubber septum. The catalyst mixture was transferred into a 25 mL Schlenk flask which contained a magnetic stirbar and an additional 0.2 mL of benzene was added to the vial to rinse any remaining material into the Schlenk flask. The flask was capped with septum, removed from the glovebox, and filled with one atm of hydrogen after one "freeze-pump-thaw" degassing cycle. The benzene solution of substrate and *tert*-butanol was transferred into the flask via a cannula. The resulting solution was stirred under H_2 at room temperature

for 20 h. After work–up, the crude ^{1}H NMR spectrum showed complete conversion. The *trans*-4-*tert*-butylcyclohexan-1-ol and *cis*-4-*tert*-butylcyclohexan-1-ol products were formed in a ratio of 1 : 1. The products were isolated via short path silica gel flash chromatography (6 : 1 pentane/ether) giving the inseparable *trans*-4-*tert*-butylcyclohexan-1-ol and *cis*-4-*tert*-butylcyclohexan-1-ol (0.047 g, 94%). The alcohol products were identified by comparison to an authentic samples.

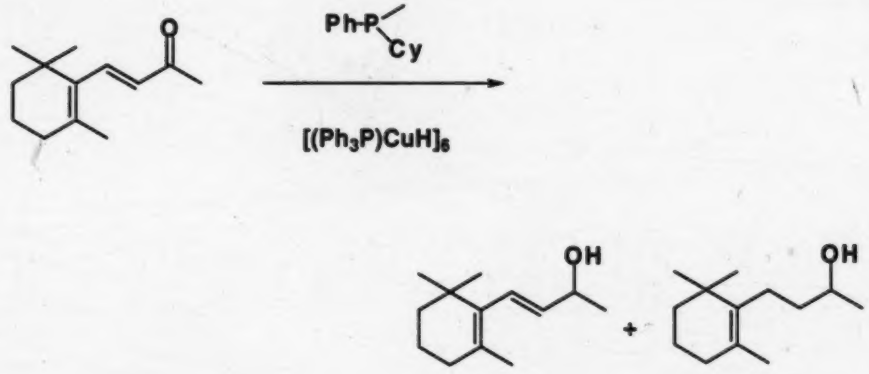
Reduction of 3,5-dimethylcyclohexenone with copper(I) chloride and added racemic methylphenylpropylphosphine.



In the glove box, a high-pressure autoclave containing a magnetic stir bar was charged with CuCl (1.6 mg, 0.016 mmol), NaO^{t}Bu (1.5 mg, 0.016 mmol), methylphenylpropylphosphine (16 mg, 0.096 mmol), *tert* -butanol (48 mg, 0.65mmol), C_6H_6 (0.6 mL), and 3,5-dimethylcyclohexenone (0.040 g, 0.32 mmol). When the CuCl, NaO^{t}Bu and phenylmethylpropylphosphine were mixed in benzene, the solution was initially colorless. Upon addition of the *tert*-butanol and 3,5-dimethylcyclohexenone, the solution color changed to orange–yellow. The combined solution was stirred under 500 psi pressure of hydrogen for 20 h. After work–up, the crude ^{1}H NMR spectrum showed complete conversion, giving the corresponding allylic alcohol and saturated alcohol products in a ratio of 2.2 : 1. The allylic alcohol consists of two isomers, trans OH : cis

OH = 88 : 12, and the saturated alcohol also consists of two isomers, trans OH : cis OH = 46 : 54. The products were isolated via short path silica gel flash chromatography (3 : 1 hexane/ethyl acetate), giving the inseparable allylic alcohol and saturated alcohol products (0.036 g, 90%). The alcohol products were identified by comparison of their ^{1}H NMR spectra to those of commercially available standards or to authentic samples prepared by unambiguous means (vide supra).

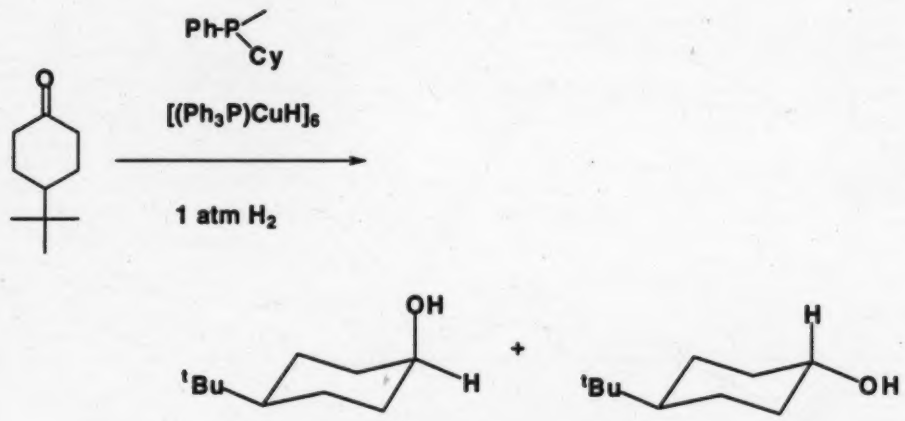
Reduction of β–ionone with added cyclohexylmethylphenylphosphine.



$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), cyclohexylmethylphenylphosphine (0.020 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol), and β-ionone (0.062 g, 0.32 mmol) were combined in benzene-d_6 as described in the general procedure (Conditions C). When the cyclohexylmethylphenylphosphine was mixed with $[(Ph_3P)CuH]_6$ in benzene-d_6 (0.8 mL), the solution color did not change. The resulting mixture solution was stirred under 500 psi pressure of hydrogen for 24 h. The crude ^{1}H NMR spectrum showed complete conversion and the corresponding allylic alcohol and saturated alcohol products were formed in a ratio of 20 : 1. The products

were isolated via short path silica gel flash chromatography (10 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and saturated alcohol products (0.055 g, 87%).

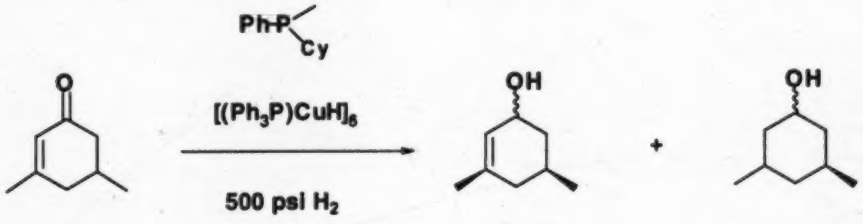
Reduction of 4-*tert*-butylcyclohexanone with added cyclohexylmethylphenylphosphine under one atomsphere pressure of hydrogen.



In the glove box, $[(Ph_3P)CuH]_6$ (0.026 g, 0.0135 mmol, 5 mol% Cu), benzene (0.5 mL), and cyclohexylmethylphenylphosphine (0.020 g, 0.097 mmol) were placed into a small vial. *Tert*-butanol (0.048 g, 0.65 mmol), benzene (0.6 mL), and 4-*tert*-butylcyclohexanone (0.049 g, 0.32 mmol) were added into another small vial which was capped with septum. The catalyst solution was transferred into a 25 mL Schlenk flask, which contained a magnetic stirbar, and an additional 0.2 mL of benzene was added to the vial to rinse any remaining material into the Schlenk flask. The flask was capped, removed from the glovebox, and filled with one atm of hydrogen after one "freeze-pump-thaw" degassing cycle. The benzene solution of substrate and *tert*-butanol was then transferred into the flask via cannula. The resulting reaction mixture was stirred under H_2 at room temperature for 24 h. After work–up, the crude ^1H NMR spectrum showed the

presence of starting material, *trans*-4-*tert*-butylcyclohexan-1-ol and *cis*-4-*tert*-butylcyclohexan-1-ol in a ratio of 29 : 23 : 48. The products were isolated via short path silica gel flash chromatography (6 : 1 pentane/ether) giving the inseparable *trans*-4-*tert*-butylcyclohexan-1-ol and *cis*-4-*tert*-butylcyclohexan-1-ol (0.034 g, 70%). The starting material and alcohol products were identified by comparison of their ^{1}H NMR spectra to that of authentic samples.

Reduction of 3,5-dimethylcyclohexenone with added cyclohexylmethylphenylphosphine.



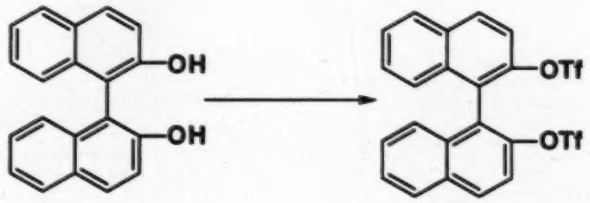
$[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), cyclohexylmethylphenylphosphine (0.020 g, 0.097 mmol), *tert*-butanol (0.048 g, 0.65 mmol), and 3,5-dimethylcyclohexenone (0.040 g, 0.32 mmol) were combined in benzene as described in the general procedure (Conditions C). The reaction solution was stirred under 500 psi pressure of hydrogen for 21 h. After work–up, the crude ^{1}H NMR spectrum showed complete conversion and the allylic alcohol and saturated alcohol products were formed in a ratio of 3 : 1. The allylic alcohol consists of two isomers: trans OH : cis OH = 83 : 17; the saturated alcohol also consists of two isomers: trans OH : cis OH = 67 : 33. The products were isolated via short path silica gel flash chromatography (3 : 1 hexane/ethyl acetate) giving the inseparable allylic alcohol and

saturated alcohol products (0.035 g, 88%). The alcohols were identified by comparison of their ^1H NMR spectra to those of commercially available standards or to authentic samples (*vide supra*).

5. Racemic binaphthyldimethylphosphine

a. Synthesis of racemic binaphthyldimethylphosphine

Synthesis of 2,2'-bis-(trifloromethanesulfonyloxy)-1,1'-binaphthyl 24.

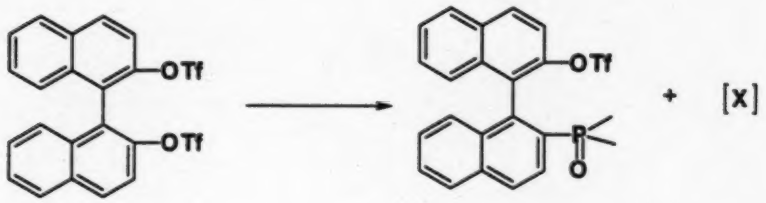


23 **24**

The synthesis of this compound was based on Uozumi's method[85] with slight modification in the reaction time and purification process. To a solution of racemic 1,1'-binaphthol **23** (1.43 g, 5.0 mmol) and pyridine (1.2 mL, 14.8 mmol) in CH_2Cl_2 was added trifluoromethanesulfonic anhydride (3.35 g, 11.9 mmol) at 0 °C, and the mixture was stirred for 2 h. The solvent was evaporated under reduced pressure, and the residue was diluted with 20 mL ethyl acetate and washed sequentially with 1 N HCl, saturated sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure; the residue was separated by short path silica gel

flash chromatography (1 : 1 CH_2Cl_2/hexanes) giving the bis(triflate) **24** as a white solid (2.58 g, 94%).

Synthesis of 2-dimethylphosphinyl-2'-trifloromethanesulfonyloxy-1,1'-binaphthyl 25.

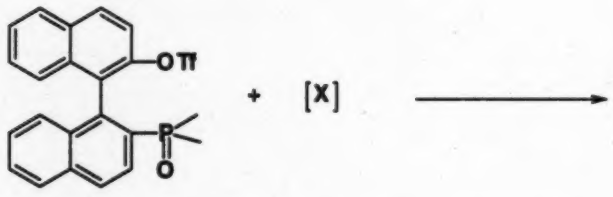


24 **25** **27**

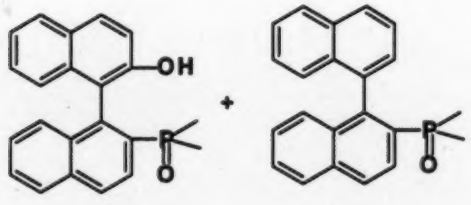
2,2'-bis-(trifloromethanesulfonyloxy)-1,1'-binaphthyl **24** (1.25 g, 2.26 mmol), DMSO (5 mL), dimethylphosphine oxide (0.35 g, 4.52 mmol, prepared by the literature method[177]), disopropylethylamine (1.16 g, 9.04 mmol), and sodium formate (0.031 g, 0.46 mmol) were combined in a 50 mL Schlenk flask containing a magnetic stirbar. Palladium(II) acetate (0.052 g, 0.23 mmol), 1,3-bis(diphenylphosphino)propane (0.095 g, 0.23 mmol), and DMSO (3 mL) were added to a small vial. The resulting solution in the small vial was then transferred to the Schlenk flask and an additional 0.5 mL of DMSO was added to the vial to rinse any remaining material into the Schlenk flask. After applying a slight vacuum and refilling with nitrogen, the reaction mixture was stirred and heated to 90 - 100 °C for 3 h, during which time the solution color changed from yellow to brown. After cooling to room temperature, the solution was concentrated under reduced pressure and the residue was diluted with ethyl acetate (30 mL), washed with water (3x40 mL) and brine and dried over sodium sulfate. The solvent was evaporated *in vacuo* and the residue was separated by flash silica gel chromatography, giving a light

yellow solid (0.95 g). Although the TLC showed only one spot, the spectroscopic data revealed that the product is a mixture of two compounds : ^{31}P NMR spectrum showed two resonances at δ 43.8 and 37.5 ppm and HRMS showed the desired molecular cation [($C_{23}H_{18}O_4F_3PS$) 478.06095, calcd. 478.06155] along with another major peak of molecular weight M^+- OTf. At that moment, it was speculated that the desired product was formed, but mixed with another unknown phosphine compound. Attempts to separate these two compounds were not successful. Thus, the mixture was used directly in the next step of the synthetic sequence.

Synthesis of 2-dimethylphosphinyl-2'-hydroxy-1,1'-binaphthyl 26 and 2-dimethylphosphinyl-1,1'-binaphthyl 27.



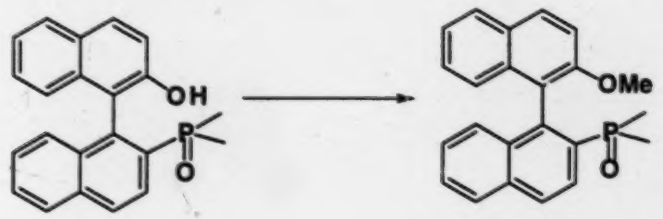
25 27



26 27

To above mixture (800 mg) in a combined solvent of dioxane (10 mL) and methol (5 mL) was added a aqueous solution of NaOH (3N, 22.5 mL). The resulting solution was stirred at room temperature for 8h. TLC showed that some starting material still remained, but upon heating at 80 °C for 2 h, no further reaction was observed by TLC analysis. The solution was cooled to room temperature and quenched with concentrated HCl. The solution was acidified by adding HCl until pH 1, followed by extraction using ethyl acetate (several portions). The extractions was dried over sodium sulfate and the solvent was evaporated *in vacuo* and the residue was separated by a silica gel flash chromatography, eluting with a solvent mixture of chloroform and methanol (20 : 1), to afford 2-dimethylphosphinyl-2'-hydroxy-1,1'-binaphthyl **26** (0.36 g, 81%) as a white solid, along with 2-dimethylphosphinyl-1,1'-binaphthyl **27** (0.18 g, quantitative) as a soft yellow solid. Data for **26**: R_f 0.2 ($CHCl_3$-MeOH 20 : 1); FTIR (KBr) 2400-3400 (br s), 1622 (m), 1584 (w), 1502 (m), 1434 (m), 1365 (s), 1299 (m), 1275 (w), 1166 (s), 1066 (w), 976 (s), 908 (s), 865 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 2 H), 7.95 (m, 2 H), 7.85 (m, 1 H), 7.57 (m, 2 H), 7.30 (m, obscured by solvent peak), 7.15 (m, 2 H), 6.67 (m, 1 H), 1.40 (m, 3 H), 1.20 (m, 3 H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 47.2; HRMS calcd. *m/z* for $C_{22}H_{19}O_2P$ 346.11227, found 346.11208. Data for 2-dimethylphosphinyl-1,1'-binaphthyl **27**: R_f 0.35 ($CHCl_3$-MeOH 20 : 1); FTIR (KBr) 3439 (br w), 3053 (w), 1504 (w), 1383 (w), 1298 (w), 1176 (s), 1027 (w), 950 (s), 903 (m), 862 (m), 820 (m), 774 (m), 748 (m), 708 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (m, 1 H), 8.05 (m, 1 H), 7.95 (m, 2 H), 7.40-7.65 (m, 6 H), 7.31 (m, 1 H), 7.15 (m, 1 H), 7.05 (m, 1 H), 1.51 (d, J = 11.6 Hz, 3 H), 1.00 (d, J = 11.6 Hz, 3 H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 43.7; HRMS calcd. *m/z* for $C_{22}H_{19}OP$ 330.11734, found 330.11661.

Synthesis of 2-dimethylphosphinyl-2'-methoxy-1,1'-binaphthyl 29.



28 **29**

To a solution of 2-dimethylphosphinyl-2'-hydroxy-1,1'-binaphthyl **28** (346 mg, 1.0 mmol) in acetone (15 mL) was added potassium carbonate (552 mg, 4.0 mmol) and methyl iodide (568 mg, 4 mmol). The resulting solution was heated to reflux for 16 h. TLC analysis showed that the reaction was not complete, so more methyl iodide (568 mg, 4 mmol) was added to the reaction mixture. After heating to reflux for an additional 8 h, the solution was cooled to room temperature, filtered, and the residue washed with diethyl ether (5 mL). The ether washes were combined with the filtrate and the resulting solution was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography, eluting with a solvent mixture of chloroform and methanol (10 : 1) to afford 2-dimethylphosphinyl-2'-methoxy-1,1'-binaphthyl **29** (340 mg, 94%) as a pale yellow solid. R_f 0.6 ($CHCl_3$-MeOH 10 : 1); FTIR (KBr) 3441 (br w), 3054 (w), 3004 (w), 2840 (w), 1556 (m), 1417 (m), 1297 (s), 1175 (s), 1117 (m), 1019 (w), 786 (m), 709 (m), 627 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (m, 1 H), 8.10 (m, 2 H), 7.90 (m, 2 H), 7.55 (m, 1 H), 7.40 (m, 1 H), 7.30 (m, 1 H), 7.25 (m, obscured by solvent peak), 7.11 (m, 1 H), 6.70 (m, 1 H), 3.75 (s, 3 H), 1.45 (d, J_{P-H} = 13.0 Hz, 3 H), 0.95 (d, J_{P-H}= 13.0 Hz, 3 H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.7. HRMS calcd. *m/z* for $C_{23}H_{21}O_2P$ 3360.12793, found 360.12759.

Synthesis of 2-(dimethylphosphino)-2'-methoxy-1,1'-binaphthyl 30.

29 **30**

To a cold (0°C) solution of 2-dimethylphosphinyl-2'-methoxy-1,1'-binaphthyl **29** (210 mg, 0.58 mmol) and triethylamine (1172 mg, 11.6 mmol) in xylene (10 mL) was added cold (0°C) trichlorosilane (405 mg, 3 mmol) dropwise. The resulting solution was allowed to warm to room temperature and then heated at 120 °C for 2 h. After cooling to room temperature, the reaction solution was diluted with diethyl ether (10 mL) and quenched with 5 mL saturated sodium bicarbonate. The resulting solution was filtered through a pad of celite and the organic layer was dried over sodium sulfate. The solvent was evaporated *in vacuo* and the residue was purified by flash silica gel chromatography under a nitrogen atmosphere, eluting with a mixture solvent of hexane and ethyl acetate (10 : 1) to afford 2-(dimethylphosphino)-2'-methoxy-1,1'-binaphthyl **30** (150 mg, 75%) as a white solid. R_f 0.4 (hexane/ethyl acetate 10 : 1); FTIR (KBr) 3052 (w), 3004 (w), 2954 (w), 2932 (w), 2835 (w), 1620 (w), 1508 (s), 1414 (w), 1331 (s), 1215 (w), 1118 (s), 907 (m), 784 (s), 703 (s), 674 (w) cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.70–7.85 (m, 5 H), 7.45 (m, 1 H), 7.18 (m, obscured by solvent peak), 6.90-7.11 (m, 4 H), 3.25 (s, 3 H), 1.12 (d, J = 3.7 Hz, 3 H), 0.92 (d, J = 3.7 Hz, 3 H); ^{31}P NMR (162 MHz, C_6D_6) δ −55.3; HRMS calcd. *m/z* for $C_{23}H_{21}OP$ 3344.13300, found 344.13277.

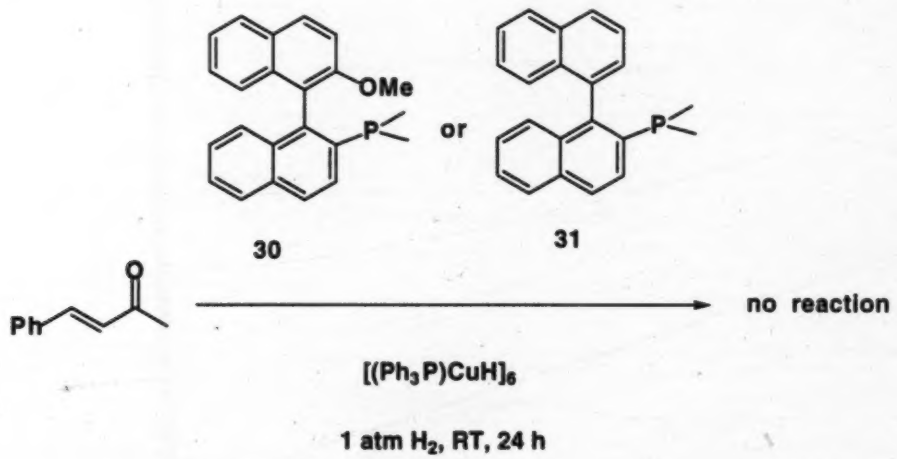
Synthesis of 2-(dimethylphosphino)-1,1'-binaphthyl 31.

27 31

Identical to above procedure, 2-dimethylphosphinyl-1,1'-binaphthyl **27** (150 mg, 0.46 mmol), triethylamine (919 mg, 9 mmol), xylene (10 mL) and trichlorosilane (310 mg, 2.3 mmol) were combined as described. The resulting solution was allowed to warm to room temperature and then heated at 120 °C for 2 h. After work-up as above, the product 2-(dimethylphosphino)-1,1'-binaphthyl **31** was obtained as a pale yellow solid (126 mg, 88%). R_f 0.7 (hexane/ethyl acetate 10:1); FTIR (KBr) 3053 (m), 3006 (w), 2955 (m), 2925 (m), 2898 (m), 1591 (w), 1554 (w), 1414 (m), 1316 (m), 1232 (m), 1137 (m), 1042 (m), 962 (s), 703 (s), 673 (s) cm^{-1}; ^1H NMR (360 MHz, C_6D_6) δ 7.82 (m, 1 H), 7.61–7.75 (m, 4 H), 7.35 (m, 4 H), 7.19 (m, 2 H, a little obscured by solvent peak), 6.98 (m, 2 H), 1.04 (d, J = 4.8 Hz, 3 H), 0.83 (d, J = 4.8 Hz, 3 H); ^{31}P NMR (162 MHz, C_6D_6) δ –57.6; HRMS calcd. *m/z* for $C_{22}H_{19}P$ 314.12244, found 314.12108.

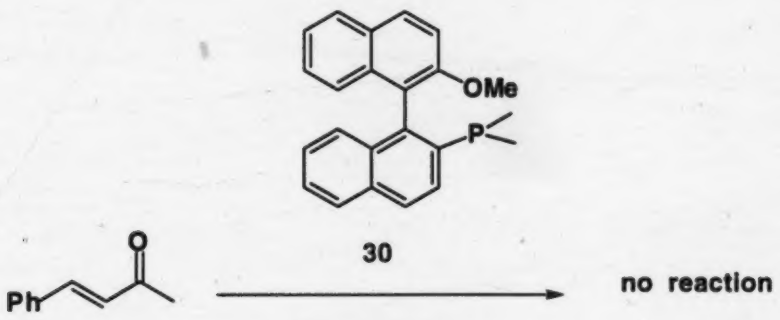
b. Reduction of α,β–unsaturated carbonyl compounds with added binaphthyldimethylphosphine

Reduction of *trans*-4-phenyl-3-buten-2-one with 2-(dimethylphosphino)-2'-methoxy-1,1'-binaphthyl 30 or 2-(dimethylphosphino)-1,1'-binaphthyl 31 derived catalysts.



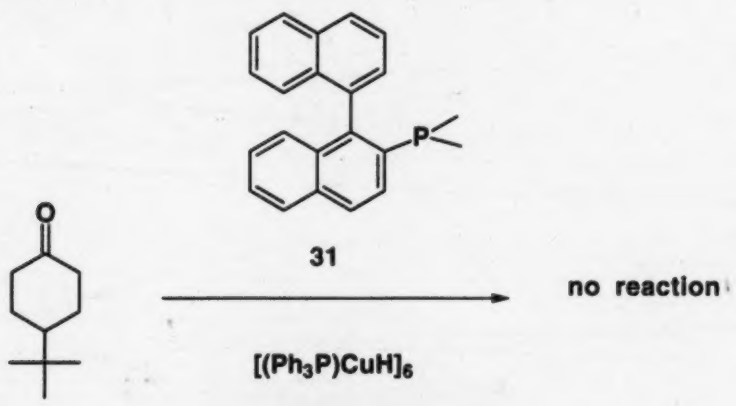
In the glove box, $[(Ph_3P)CuH]_6$ (0.0053 g, 0.0027 mmol, 5 mol% Cu), benzene (0.4-0.8 M in substrate), 2-(dimethylphosphino)-2'-methoxy-1,1'-binaphthyl **30** (22 mg, 0.065 mmol) or 2-(dimethylphosphino)-1,1'-binaphthyl **31** (20 mg, 0.065 mmol), *tert*-butanol (0.048 g, 0.65 mmol) were placed into a small vial. *Trans*-4-phenyl-3-buten-2-one (0.047 g, 0.32 mmol) was then added and the mixture solution was transferred into a 25 mL Schlenk flask containing a magnetic stirbar. An additional 0.2 mL of benzene was added to the vial to rinse any remaining material into the Schlenk flask. The flask was capped, removed from the glovebox, and filled with one atm of hydrogen after one "freeze-pump-thaw" degassing cycle. The solution was stirred under one atm of H_2 at room temperature for 24 h. After general work–up, the crude ^1H NMR spectrum showed that no reduction occured.

Reduction of *trans*-4-phenyl-3-buten-2-one with 2-(dimethylphosphino)-2'-methoxy-1,1'-binaphthyl 30 and CuCl derived catalyst.



CuCl (0.4 mg, 0.004 mmol), NaO^{t}Bu (0.4 mg, 0.004 mmol), 2-(dimethylphosphino)-2'-methoxy-1,1'-binaphthyl **30** (8.3 mg, 0.024 mmol), *tert*-butanol (12 mg, 0.16 mmol) and *trans*-4-phenyl-3-buten-2-one (0.012 g, 0.08 mmol) were combined in C_6H_6 (0.6 mL). The resulting mixture was transferred to a glass liner containing a magnetic stirbar, which was then sealed inside a stainless steel high pressure autoclave. The sealed vessel was removed from the glove box, connected to a hydrogen cylinder, flushed several times by pressurizing with H_2 and releasing the pressure and then charged with H_2 up to 500 psi. Stirring was initiated after pressurization and after 19 h, the pressure was released and the vessel was opened to air. After stirring for several minutes, the resulting suspension was filtered though a pipette filled with cotton and celite and washed with a little reaction solvent. The solvent was evaporated *in vacuo* and the residue was taken up into C_6D_6 for ^1H NMR spectroscopic analysis. The ^1H NMR showed that no reduction occured.

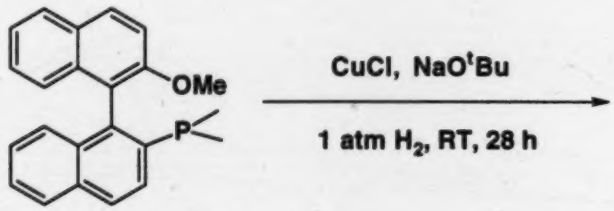
Reduction of 4-*tert*-butylcyclohexanone with 2-(dimethylphosphino)-1,1'-binaphthyl 31 derived catalyst under 500 psi of H_2 and 50°C.



In the glove box, $[(Ph_3P)CuH]_6$ (0.0026 g, 0.0013 mmol, 5 mol% Cu), benzene (0.4-0.8 M in substrate), 2-(dimethylphosphino)-1,1'-binaphthyl **31** (10 mg, 0.032 mmol), *tert*-butanol (0.024 g, 0.32 mmol) were placed into a small vial. 4-*tert*-butylcyclohexanone (0.025 g, 0.16 mmol) was then added and the mixture solution was transferred into a glass liner containing a magnetic stirbar, which was then sealed inside a stainless steel high pressure autoclave. The sealed vessel was removed from the glove box, connected to a hydrogen cylinder, flushed several times by pressurizing with H_2 and releasing the pressure and then charged with H_2 up to 500 psi. The sealed vessel was then put into a 50 °C sand bath. Stirring was initiated and after 19 h at 50 °C, the vessel was cooled to room temperature. The pressure was released and the vessel was opened to air; at this time some black precipitate was found at the bottom of the glass liner. After work–up as above, The ^1H NMR showed that no reduction occured.

c. Catalyst investigation.

2-(dimethylphosphino)-2'-methoxy-1,1'-binaphthyl 30 and CuCl derived catalyst.



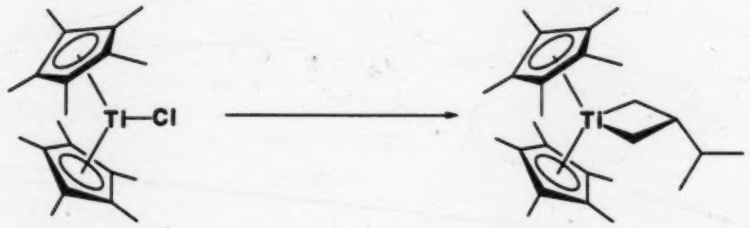
30

CuCl (0.4 mg, 0.004 mmol), NaO^{t}Bu (0.4 mg, 0.004 mmol), and 2-(dimethylphosphino)-2'-methoxy-1,1'-binaphthyl **30** (5.6 mg, 0.016 mmol) were combined in C_6D_6 (0.6 mL). The resulting mixture was transferred to a 25 mL Schlenk flask containing a magnetic stirbar. An additional 0.2 mL of benzene–d_6 was added to the vial to rinse any remaining material into the Schlenk flask. The flask was capped, removed from the glovebox, and filled with one atm of hydrogen after one "freeze-pump-thaw" degassing cycle. The solution was stirred under one atm of H_2 at room temperature for 28 h, and the solution color changed from colorless to light–yellow. The resulting solution was transfered into a NMR tube for spectroscopic analysis. ^{31}P NMR spectrum showed two new peaks at δ –35.6 and 36.5 ppm.

PART TWO: FREE RADICAL ALKYLATION OF TITANIUM(III) ALLYL AND PROPARGYL COMPLEXES.

A. An Improved Method For The Synthesis of Titanacyclobutane Complexes

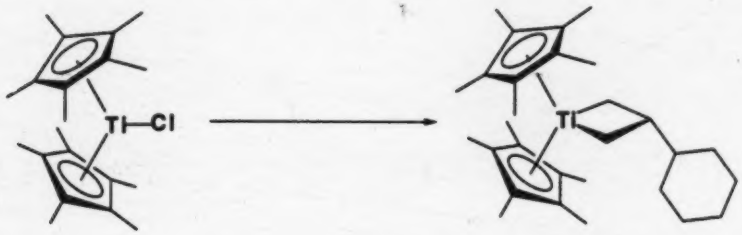
1,1-Bis(pentamethylcyclopentadienyl)-3-isopropyltitanacyclobutane 70



70

In the drybox, to a solution of Cp^*_2TiCl (17.7 mg, 0.05 mmol) in THF (1mL) cooled to -35 °C was added a solution of allyl bromide (6 mg, 0.05 mmol) in THF (1mL), also maintained at -35 °C. The solution immediately turned red. After shaking for about 1 min, a solution of SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol) was added at -35 °C and the resulting solution was treated with a solution of isopropyl iodide (8.5 mg, 0.05 mmol) in THF (1mL) at -35 °C. The dark blue reaction mixture was allowed to warm slowly to room temperature, shaking occasionally as the temperature rose. After stirring at room temperature for 22 h, the solution turned dark brown. The volatiles were removed *in vacuo* and the residue was triturated with pentane and filtered through a plug of celite. Evaporation of solvent from the filtrate under reduced pressure gave 1,1-bis(pentamethylcyclopentadienyl)-3-isopropyltitanacyclobutane complex **70** as a dark-red oil (19.2 mg, 96%). The recovered material was spectroscopicaly homogeneous and identical to the previously characterized complex.[97]

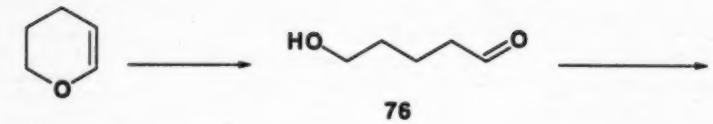
1,1-Bis(pentamethylcyclopentadienyl)-3-cyclohexyltitanacyclobutane 71.



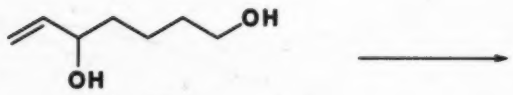
71

In the drybox, to a solution of Cp^*_2TiCl (17.7 mg, 0.05 mmol) in THF (1mL) at -35 °C was added a solution of allyl bromide (6 mg, 0.05 mmol) in THF (1mL), also at -35 °C. The solution immediately turned red and, after shaking for about 1 min, a solution of SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol) was added at -35 °C. A solution of cyclohexyl iodide (10.5 mg, 0.05 mmol) in THF (1mL) was then added at -35 °C. The reaction mixture was allowed to warm to room temperature and then transferred into a glass bomb and heated at 50°C for 6 h. During this time the solution turned dark brown. The reaction mixture was cooled to room temperature, the volatiles were removed *in vacuo*, and the residue was triturated with pentane and then filtered through a plug of celite. Evaporation of solvent under reduced pressure gave 1,1-bis(pentamethylcyclopentadieny)-3-cyclohexyltitanacyclobutane **73** as a dark-red oil (21 mg, 95%). The recovered material was spectroscopically homogeneous and identical to the previously characterized complex.[97]

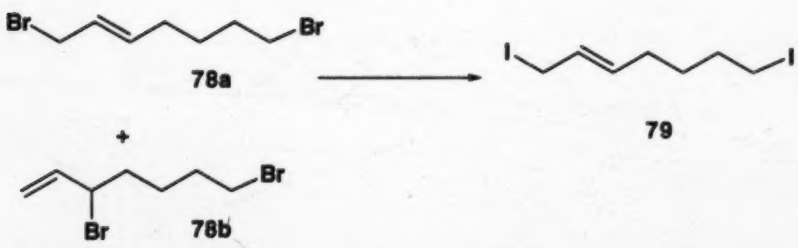
1,7-Diiodo-hept-2-ene 79.



76



77



The first step of this synthesis was based on Woods' method, with slight modification.[154] To a solution of water (30 mL) and concentrated HCl (2.5 mL) was added 2,3-dihydropyran (10 g, 0.12 mol) and the resulting solution was stirred for 40 minutes. Two drops of phenolphthalein was then added and the solution was neutralized by enough NaOH (20% aqueous) until the pink color persisted. The solution was extracted several times with ether (it should be noted that the extraction step requires prolonged shaking to obtain a better yield). The ether extractions were combined, washed with brine, and dried over sodium sulfate. After evaporation of the solvent, the residue was distilled under reduced pressure. The product was collected as a colorless oil at 80°C/10 mm (8.6 g, 72%) and used without further characterization.

To a solution of vinyl magnesium bromide (1.0 M in THF, 30mL, 30 mmol) at 0°C was added slowly a solution of the above oil (1.02 g, 10 mmol) in THF (5 mL). The reaction solution was stirred at 0°C for 10 minutes and then warmed to room temperature. After 2 h of stirring at room temperature, the solution was cooled to 0°C again and treated with saturated aqueous NH_4Cl (10mL). The suspension was filtered and the salts were washed with ether. The filtrate and the washes were combined, washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by flash silica gel chromatography eluting with ethyl acetate giving dialcohol **77** (0.88 g, 68%) as a colorless oil. This material was carried on without further characterization.

To a solution of the above product (260 mg, 2 mmol) in ether (5 mL) was added dropwise a solution of PBr_3 in ether (4 mL). The reaction mixture turned first to cloudy white and then became clear. After stirring overnight at room temperature, the color of the solution had changed to brown. The resulting solution was quenched with water (5 mL) and extracted with several portions of ether. The combined ether extraction was washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent *in vacuo*, the residue was purified by flash silica gel chromatography eluting with a solvent mixture of ethyl acetate and hexane (v/v 1 : 10) to give a colorless liquid (260 mg, 51%). The product (170 mg, 0.66 mmol) was taken up into acetone (8 mL) and treated with NaI (400 mg, 2.66 mmol). The solution was heated to reflux for 3 h and after cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was purified by flash silica gel chromatography eluting with a solvent mixture of ethyl acetate and hexane (v/v 1 : 10) giving 1,7-diiodo-hept-2-ene **79** as a colorless liquid (200 mg, 87%).[178] ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (m, 2 H), 3.88 (m, 2 H), 3.19 (t, J = 6.8 Hz, 2 H), 2.02–2.15 (m, 2 H), 1.76–1.96 (m, 2 H), 1.43-1.59 (m, 2 H).

Attempted synthesis of 7,7-bis(*tert*-butylcyclopentadienyl)-titanabicyclo[4.2.0]octane 80.

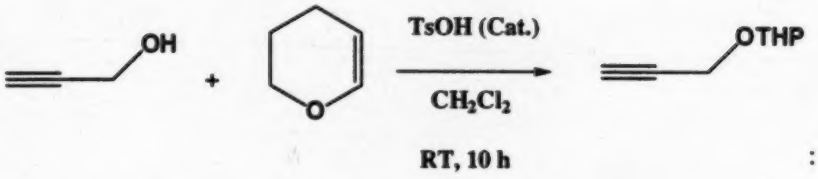
79 80

In the drybox, to a solution of $[^tBuCp_2TiCl]_2$ (16.3 mg, 0.025 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol, 3 equiv) at -35 °C, resulting in a dark blue solution. A solution of 1,7-diiodo-hept-2-ene (17.5 mg, 0.05 mmol) in dry THF (1 mL) was then added to the reaction mixture at -35 °C. The solution was shaken occasionally as the temperature rose to room temperature. The reaction mixture was maintained at room temperature for 1 h, shaking occasionally. No color change was observed. The solution was then transferred into a glass bomb and heated at 60°C for 5 h. The resulting mixture was cooled to room temperature. The volatiles was removed *in vacuo* and the residue were triturated with pentane and then filtered through a plug of celite. Evaporation of solvent from the filtrate under reduced pressure gave a dark oil. Analysis of the crude mixture by ^1H NMR spectroscopy found some tentatively assigned desired product **80** (in very low yield), which could not be separated from the crude mixture. ^1H NMR (360 MHz, C_6D_6, selected data only) δ 6.12 (s, 1 H), 6.05 (s, 1 H), 5.45 (d, 2 H), 5.30 (s, 1 H), 5.22(s, 1 H), 5.19 (s, 1 H), 5.10 (s, 1 H), 2.70 (t, 1 H), 2.35 (m), 1.15 (br s), 1.07(br s), -0.21(m, 1 H).

B. Intramolecular Free Radical Cyclizations of Titanium(III) Propargyl Complexes

1. Organic substrate synthesis

2-prop-2-ynyloxytetrahydropyran.



To a solution of propargyl alcohol (58 mL) in CH_2Cl_2 (400 mL) was added slowly a solution of P-TsOH (catalytic amount) and 3,4- dihydro-2H-pyran (109 mL) in CH_2Cl_2 (100 mL); the resulting solution was stirred for 10 h. The reaction mixture was treated with 1M NaOH solution (10 mL) and then extracted several times with CH_2Cl_2. The combined extractions was dried over sodium sulfate and fitered. After evaporation of solvent, the residue was distilled under vacuum (60 °C / 20 torr), giving the product 2-prop-2-ynyloxy-tetrahydro-pyran as a colorless liquid (127 mg, 91%).

1.6-Dibromo-hex-2-yne 91.

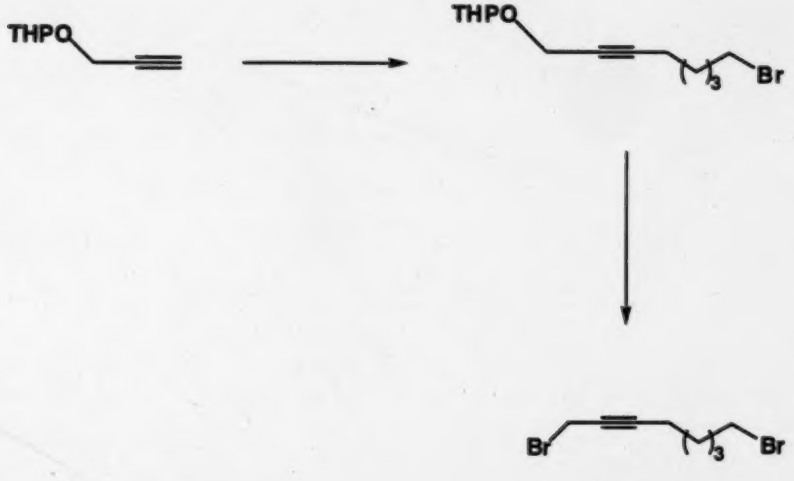
91

To a stirred solution of the above 2-prop-2-ynyloxy-tetrahydro-pyran (0.7 g, 5 mmol) in anhydrous liquid NH_3 (30mL, condensed at -78°C with a dry ice / acetone condenser) was added dropwise a solution of BuLi (1.6 M in hexane, 3.2 mL, 5 mmol, 1 equiv) at -78°C. The cooling bath was removed and the resulting reaction mixture was stirred and maintained at reflux for about 0.5 h. The resulting solution was treated with 1,3-dibromopropane (1.01 g, 5 mmol, 1 equiv) by dropwise addition and the liquid ammonia was allowed to evaporate slowly. After stirring for 3 h, all of the ammonia had evaporated and the residue was treated with a mixture of ether and water (60 mL/20 mL). The resulting organic phase was washed with water and brine (20mL each) and dried over $NaSO_4$. Evaporation of the solvent under reduced pressure gave a light yellow oil, which was purified by flash silica gel chromatography, eluted with a solvent mixture of chloroform-methanol (v/v 20 : 1) to give a colorless oil (0.35g, 25%).

A solution of above product (0.20 g) in CH_2Cl_2 (4 mL) was added to a ice cold CH_2Cl_2 solution (10 mL) of triphenylphosphine dibromide, prepared from Br_2 (0.24 g, 1.5 mmol) and triphenylphosphine (0.39 g, 1.5 mmol) at 0°C over 10 min. The reaction mixture was stirred for 20 h at room temperature. The resulting solution was poured into a stirred solution of hexane (40 mL). The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The crude product was purified by

flash column chromatography eluted with a solvent mixture of hexanes and ethyl acetate (v/v 10 : 1), giving 1.6-dibromo-hex-2-yne **91** as colorless oil. (168 mg, 86%). Spectroscopic data for the compound **91:** FTIR (KCl) 3002 (w), 2960 (m), 2840 (w), 2233 (m), 1350 (m), 1328 (w), 1270 (s), 1153 (w), 853 (w), 569 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (t, J = 2.3 Hz, 2 H, H_1), 3.39 (t, J = 6.6 Hz, 2 H, H_6), 2.33 (tt, J = 6.6; 2.3 Hz, 2 H, H_4), 1.93 (quintet, J = 6.6 Hz, 2 H, H_5); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 85.5 (C_2), 76.5 (C_3), 32.2 (C_1), 31.1 (C_6), 17.7 (C_4), 15.2 (C_5); HRMS calcd. *m/z* (M+1) for $C_6H_9{}^{81}Br_2$ 242.9030, $C_6H_9{}^{79}Br{}^{81}Br$ 240.9050, $C_6H_9{}^{79}Br_2$ 238.9071, found $C_6H_9{}^{81}Br_2$ 242.9020, $C_6H_9{}^{79}Br{}^{81}Br$ 240.9040, $C_6H_9{}^{79}Br_2$ 238.9061.

1,8-Dibromo-oct-2-yne 92.



92

General procedure for mono–alkylation and bromination. To a stirred solution of the above 2-prop-2-ynyloxy-tetrahydro-pyran (2.8 g, 20 mmol) in liquid NH_3 (50mL, condensed at -78°C with a dry ice / acetone condenser) was added dropwise a

solution of BuLi (1.6 M in hexane, 12.5 mL, 20 mmol, 1 equiv) at -78°C. The cooling bath was removed and the resulting reaction mixture was stirred and maintained at reflux for about 0.5 h. The resulting solution was treated with 1,5-dibromopentane (4.6 g, 20 mmol, 1 equiv) by dropwise addition and the liquid ammonia was allowed to evaporate slowly. After stirring for 3 h, all of the ammonia had evaporated and the residue was treated with a mixture of ether and water (120 mL/40 mL). The resulting organic phase was washed with water and brine (50mL each) and dried over $NaSO_4$. Evaporation of the solvent under reduced pressure gave a light yellow oil, which was purified by flash silica gel chromatography, eluted with a solvent mixture of chloroform-methanol (v/v 20 : 1) to give a colorless oil (3.64 g).

A solution of above product (1.10 g) in CH_2Cl_2 (4 mL) was added to a ice cold CH_2Cl_2 solution (20 mL) of triphenylphosphine dibromide, prepared from Br_2 (1.2 g, 7.6 mmol) and triphenylphosphine (2.0 g, 7.6 mmol) at 0°C over 10 min. The reaction mixture was stirred for 20 h at room temperature. The resulting solution was poured into a stirred solution of hexane (150 mL). The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography eluted with a solvent mixture of hexanes and ethyl acetate (v/v 10 : 1), giving dibromooctyne **92** as a colorless oil. (0.93 g, 91%). Spectroscopic data for compound **92:** FTIR (KCl) 3002 (s), 2309 (w), 2232 (m), 1645 (w), 1332 (w), 1267 (s), 1152 (w), 863 (w), 728 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (t, J = 2.4 Hz, 2 H), 3.40 (t, J = 6.4 Hz, 2 H), 2.26 (tt, J = 6.8; 2.3 Hz, 2 H), 1.82–1.90 (m, 2 H), 1.54 (m, 4 H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 87.6, 75.7, 33.5, 32.2, 27.4, 27.3, 18.8, 15.6; HRMS calcd. *m/z* (M+1) for $C_6H_9{}^{81}Br_2$ 242.9030, $C_6H_9{}^{79}Br{}^{81}Br$ 240.9050, $C_6H_9{}^{79}Br_2$ 238.9071, found $C_6H_9{}^{81}Br_2$ 242.9020, $C_6H_9{}^{79}Br{}^{81}Br$ 240.9040, $C_6H_9{}^{79}Br_2$ 238.9061.

1.9-Dibromo-non-2-yne 93.

93

Following the general procedure, the reaction of 2-prop-2-ynyloxy-tetrahydro-pyran (700 mg, 5 mmol) with BuLi (1.6M in hexane, 3.2mL, 5 mmol, 1 equiv) and 1,6-dibromohexane (1.22 g, 5 mmol, 1 equiv) gave a colorless oil (0.77 g, 51%). The oil (227 mg) was treated with triphenylphosphine dibromide, prepared from Br_2 (264 mg, 1.65 mmol) and triphenylphosphine (432 mg, 1.65 mmol). After purification by flash column chromatography, the 1,9-dibromo-non-2-yne **93** was obtained (197 mg, 93%) as a light yellow oil. Spectroscopic data for compound **93:** FTIR (KCl) 2937 (s), 2859 (m), 2233 (m), 1460 (m), 1430 (m), 1257 (m), 1212 (m), 1154 (w), 644 (m), 609 (w), 561 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (t, J = 2.3 Hz, 2 H), 3.40 (t, J = 6.8 Hz, 2 H), 2.24 (tt, J = 6.8; 2.3 Hz, 2 H), 1.80–1.91 (m, 2 H), 1.37-1.56 (m, 6 H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 88.0, 75.6, 33.8, 32.6, 28.1, 27.9, 27.7, 18.9, 15.7; HRMS calcd. *m/z* for $C_9H_{14}{}^{81}Br_2$ 283.9421, $C_9H_{14}{}^{79}Br{}^{81}Br$ 281.9442, $C_9H_{14}{}^{79}Br_2$ 279.9462, found $C_9H_{14}{}^{81}Br_2$ 283.9425, $C_9H_{14}{}^{79}Br{}^{81}Br$ 281.9436, $C_9H_{14}{}^{79}Br_2$ 279.9465.

1.10-Dibromo-dec-2-yne 94.

94

Following the general procedure, the reaction of 2-prop-2-ynyloxy-tetrahydro-pyran (700 mg, 5 mmol) with BuLi (1.6M in hexane, 3.2mL, 5 mmol, 1 equiv) and 1,7-dibromoheptane (1.29 g, 5 mmol, 1 equiv) gave a colorless oil (0.86 g, 54%). This oil (238 mg) was treated with triphenylphosphine dibromide, prepared from Br_2 (264 mg, 1.65 mmol) and triphenylphosphine (432 mg, 1.65 mmol). After purification by flash column chromatography, the 1,10-dibromo-dec-2-yne **94** was obtained (191 mg, 86%) as a light yellow oil. Spectroscopic data for compound **94:** FTIR (KCl) 2934 (s), 2857 (s), 2233 (m), 1462 (m), 1429 (m), 1248 (m), 1210 (m), 1153 (w), 725 (w), 644 (m), 609 (w), 562 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (t, J = 2.3 Hz, 2 H), 3.40 (t, J = 6.8 Hz, 2 H), 2.24 (tt, J = 6.8; 2.3 Hz, 2 H), 1.80–1.91 (m, 2 H), 1.24-1.56 (m, 8 H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 88.1, 75.4, 33.9, 32.7, 28.6, 28.2, 28.2, 28.0, 18.9, 15.7; HRMS calcd. *m/z* for $C_{10}H_{16}{}^{79}Br^{81}Br$ 295.9598, found 295.9577.

1.11-Dibromo-undec-2-yne 95.

95

Following the general procedure, the reaction of 2-prop-2-ynyloxy-tetrahydro-pyran (700 mg, 5 mmol) with BuLi (1.6M in hexane, 3.2mL, 5 mmol, 1 equiv) and 1,8-dibromooctane (1.36 g, 5 mmol, 1 equiv) gave a colorless oil (1.02 g, 64%). This oil (200 mg) was treated with triphenylphosphine dibromide, prepared from Br_2 (192 mg, 1.20 mmol) and triphenylphosphine (314 mg, 1.20 mmol). After purification by flash column chromatography, the 1,11-dibromo-undec-2-yne **95** was obtained (168 mg, 90%) as a

colorless oil. Spectroscopic data for compound **95:** FTIR (KCl) 3002 (s), 2855 (s), 2232 (m), 1463 (m), 1428 (m), 1328 (m), 1255 (m), 1151 (w), 1089 (w), 799 (w), 723 (w), 644 (m), 561 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (t, J = 2.3 Hz, 2 H), 3.34 (t, J = 6.8 Hz, 2 H), 2.17 (tt, J = 6.8; 2.3 Hz, 2 H), 1.79 (quintet J = 7.4 Hz, 2 H), 1.15-1.50 (m, 10 H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 88.2, 75.4, 34.0, 32.8, 28.9, 28.7, 28.6, 28.3, 28.1, 18.9, 14.1; HRMS calcd. m/z $(M-Br)^+$ for $C_{11}H_{18}{}^{81}Br$ 231.0571, $C_{11}H_{18}{}^{79}Br$ 229.0592, found $C_{11}H_{18}{}^{81}Br$ 231.0568, $C_{11}H_{18}{}^{79}Br$ 229.0590.

2. Intramolecular free radical cyclizations

6,6-Bis(pentamethylcyclopentadienyl)titana-bicyclo[3.2.0]hept-1-(5)-ene 96.

96

To a cold (-78°C) solution of Cp^*_2TiCl (17.7 mg, 0.05 mmol) and SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol) in dry THF (2 mL) was added a solution of 1,6-dibromo-hex-2-yne **91** (12 mg, 0.05 mmol) in dry THF (1 mL) at -78 °C. The cooling bath was removed and the mixture was warmed to room temperature. The resulting reaction mixture was then heated at 60 °C for 18 h. During that time the colour of the solution changed from blue to brown-red. After cooling to room temperature, the solvent was evaporated *in*

vacuo and the residue was triturated with pentane. The combined extracts were filtered through a short column of celite followed by concentration to give a red oil (19 mg, 95%). 6,6-Bis(pentamethylcyclopentadienyl)titanabicyclo[3.2.0]hept-1-(5)-ene **96**. This material was spectroscopically homogeneous and was not further purified. ^{1}H NMR (600 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, and COSY spectra) δ 2.83 (m, 2 H, H_4), 2.47 (t, J = 7.3 Hz, 2 H, H_2), 2.11 (quintet, J = 7.3 Hz, 2 H, H_3), 2.06 (m, 2 H, H_7), 1.69 (br s, 30 H, C_5Me_5); ^{1}H-^{1}H GCOSY (600 MHz, C_6D_6, each correlation listed only once) δ 2.83 (H_4) ↔ 2.47 (H_2, weak), 2.11 (H_3), 2.06 (H_7, weak); 2.47 (H_2) ↔ 2.11 (H_3), 2.06 (H_7, weak); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, COSY) δ 230.0 (C_5), 117.6 ($\underline{C}_5Me_5$), 110.8 (C_1), 69.3 (C_7), 40.4 (C_4), 34.0 (C_2), 30.0 (C_3), 12.0 ($C_5\underline{Me}_5$); HMQC (600 MHz, decoupled, C_6D_6) δ 69.3 (C_7) ↔ δ 2.06 (H_7); δ 40.4 (C_4) ↔ δ 2.83 (H_4); δ 34.0 (C_2) ↔ δ 2.47 (H_2); δ 30.0 (C_3) ↔ δ 2.11 (H_3); δ 12.0 ($\underline{C}_5Me_5$) ↔ δ 1.69 ($C_5(C\underline{H}_3)_5$); HMQC (300 MHz, coupled, C_6D_6) δ 69.3 (C_7) ↔ δ 2.06 ($J_{C\text{-}H}$ = 150.3 Hz, H_7); δ 40.4 (C_4) ↔ δ 2.83 ($J_{C\text{-}H}$ = 150.3 Hz, H_4); δ 34.0 (C_2) ↔ δ 2.47 ($J_{C\text{-}H}$ = 141.0 Hz, H_2); δ 30.0 (C_3) ↔ δ 2.11 ($J_{C\text{-}H}$ = 151.9 Hz, H_3); δ 12.0 ($\underline{C}_5Me_5$) ↔ δ 1.69 ($J_{C\text{-}H}$ =124.0 Hz, $C_5(C\underline{H}_3)_5$); HMBC (600 MHz, C_6D_6, selected data only) δ 2.47 (H_2) ↔ δ 30.0 (C_3), 40.4 (C_4, weak), 110.8 (C_1), 230.0 (C_5, weak); δ 2.11 (H_3) ↔ δ 34.0 (C_2), 40.4 (C_4), 110.8 (C_1), 230.0 (C_5, weak); δ 2.06 (H_7) ↔ δ 34.0 (C_2); HRMS calcd. *m/z* for $C_{26}H_{38}Ti$ 398.2453, found 398.2424.

8,8-Bis(pentamethylcyclopentadienyl)titanabicyclo[5.2.0]non-1-(7)-ene 97.

97

Following the above procedure, to a cold solution of Cp^*_2TiCl (17.7 mg, 0.05 mmol) and SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol) in dry THF (2 mL) was added a solution of 1,8-dibromo-oct-2-yne **92** (13.4 mg, 0.05 mmol) in dry THF (1 mL) at -78 °C. The cooling bath was removed and the mixture was warmed to room temperature. The reaction mixture was then heated at 50 °C for 16 h. During that time, the colour of the solution changed from blue to brown-red. After work-up, the product **97** was obtained as a red oil (21 mg, 98%). 8,8-Bis(pentamethylcyclopentadienyl)titanabicyclo[5.2.0]non-1-(7)-ene **97**. ^1H NMR (600 MHz, C_6D_6) δ 2.43 (br s, 2 H, H_6), 2.36 (s, 2 H, H_9), 2.32 (m, 2 H, H_2), 1.72 (br s, 30 H, $C_5(CH_3)_5$), 1.68 (m, 2 H, H_4), 1.58-1.66 (m, 4 H, H_3, H_5); ^1H-^1H GCOSY (600 MHz, C_6D_6, each correlation listed only once) δ 2.43 (H_6) ↔ 1.59 (H_5), 2.36 (H_9), 2.32 (H_2); 2.32 (H_2) ↔ 1.64 (H_3); $^{13}C\{^1H\}$ NMR (75 MHz, C_6D_6, assignments confirmed by HMQC, HMBC) δ 210.9 (C_7), 117.6 ($\underline{C}_5Me_5$), 104.5 (C_1), 83.9(C_9), 35.7 (C_6), 34.7 (C_2), 32.0 (C_4), 30.4 (C_5), 28.9 (C_3), 12.0 ($C_5\underline{Me}_5$); HMQC (600 MHz, decoupled, C_6D_6) δ 83.9 (C_9) ↔ δ 2.36 (H_9); δ 35.7 (C_6) ↔ δ 2.43 (H_6); δ 34.7 (C_2) ↔ δ 2.32 (H_2); δ 32.0 (C_4) ↔ δ 1.68 (H_4); δ 30.4 (C_5) ↔ δ 1.59(H_5); δ 28.9 (C_3) ↔ δ 1.63(H_3); HMBC (600 MHz, C_6D_6, selected data only) δ 2.43 (H_6) ↔ δ 30.4 (C_5), 32.0 (C_4), 104.5 (C_1), 210.9 (C_7); δ 2.36 (H_9) ↔ δ 104.5 (C_1), 210.9 (C_7); δ 2.32

(H_2) ↔ δ 28.9 (C_3), 32.0 (C_4), 104.5 (C_1), 210.9 (C_7); HRMS calcd. *m/z* for $C_{28}H_{42}Ti$ 426.2766, found 426.2771.

9,9-Bis(pentamethylcyclopentadienyl)titanabicyclo[6.2.0]dec-1- (8)-ene 98:

98

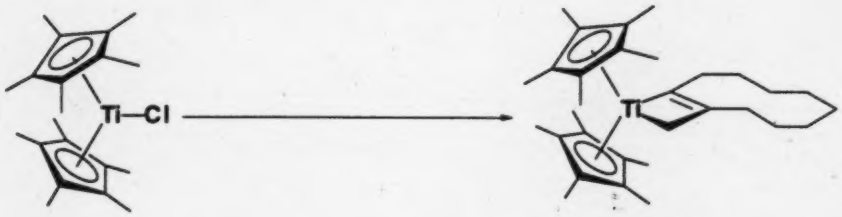
Following the general procedure, to a solution of Cp^*_2TiCl (17.7 mg, 0.05 mmol) and SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol) in dry THF (2 mL) was added a solution of 1,9-dibromo-non-2-yne **93** (14.1 mg, 0.05 mmol) in dry THF (1 mL) at -78 °C. The cooling bath was removed and the solution was warmed to room temperature. The resulting solution was heated at 60 °C for 24 h, during which time the solution colour changed from blue to brown-red. After work-up as described in the above procedure, the product **98** was obtained as a red oil (21.2 mg, 96%). Spectroscopic data for complex **98:** ^1H NMR (300 MHz, C_6D_6) δ 2.62–2.69 (m, 2 H), 2.36-2.44 (m, 4 H), 1.71-1.83 (overlapping signals, 36 H), 1.62 (m, 2 H); ^{13}C {^1H} NMR (75 MHz, C_6D_6) δ 212.0, 117.9, 105.0, 82.4, 33.6, 33.2, 30.4, 27.7, 27.3, 26.1, 12.1; HRMS calcd. *m/z* for $C_{29}H_{44}Ti$ 440.2922, found 440.2912.

10,10-Bis(pentamethylcyclopentadienyl)titanabicyclo[7.2.0]undec-1-(9)-ene 99.

99

Following the above procedure, to a solution of Cp^*_2TiCl (17.7 mg, 0.05 mmol) and SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol) in dry THF (2 mL) was added a solution of 1,10-dibromo-dec-2-yne **94** (14.5 mg, 0.05 mmol) in dry THF (1 mL) at -78 °C. The cooling bath was removed and the mixture was warmed to room temperature. The reaction mixture was then heated at 60 °C for 24 h, during which time the solution color changed from blue to brown-red. After work-up as described in the above procedure, a dark-red oil **99** (20.8 mg, 92%) was obtained. An analytical sample was prepared by crystallization from pentane at -30 °C. Spectroscopic data for complex **99:** ^1H NMR (300 MHz, C_6D_6) δ 2.52–2.61 (m, 2 H), 2.31-2.41 (m, 4 H), 1.81-1.90 (m, 8 H), 1.71-1.81 (overlapping, m, 32 H); ^{13}C $\{^1H\}$ NMR (75 MHz, C_6D_6) δ 215.5, 118.0, 105.1, 80.7, 34.7, 33.0, 29.5, 28.5, 26.9, 26.4, 22.7, 12.5; HRMS calcd. *m/z* for $C_{30}H_{46}Ti$ 454.3079, found 454.3066.

11,11-Bis(pentamethylcyclopentadienyl)titanabicyclo[8.2.0]undec-1-(10)-ene 100:



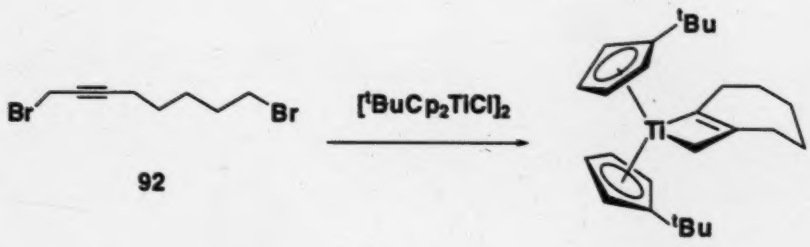
100

Following the general procedure, to a solution of Cp^*_2TiCl (17.7 mg, 0.05 mmol) and SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol) in dry THF (2 mL) was added a solution of 1,11-dibromo-undec-2-yne **95** (15.5 mg, 0.05 mmol) in dry THF (1 mL) at -78 °C. The cooling bath was removed and the mixture was warmed to room temperature, after which it was heated at 60 °C for 12 h. During that time the solution colour changed from blue to brown-red. After work-up as described in the above procedure, complex **100** (20 mg, 85%) was obtained as a dark-red oil. An analytical sample was prepared by crystallization from pentane at -30 °C. Spectroscopic data for complex **100:** ^1H NMR (300 MHz, C_6D_6) δ 2.51–2.64 (m, 2 H), 2.22-2.40 (m, 4 H), 1.74-1.82 (overlapping, m, 32 H), 1.12-1.68 (m, 10 H); $^{13}C\{^1H\}$ NMR (75 MHz, C_6D_6) δ 212.4, 117.8, 105.7, 78.4, 35.1, 32.8, 32.3, 31.6, 31.4, 31.1, 30.3, 29.5, 12.1; HRMS calcd. *m/z* for $C_{31}H_{48}Ti$ 468.3236, found 468.3230.

C. Radical Additions of Titanium (III) Propargyl Complexes Using Cp and ^{t}BuCp Templates.

a. The use of the tert–butylcyclopentadienyl template for titanacyclobutene formation.

8,8-Bis(*tert*-butylcyclopentadienyl)titanabicyclo[5.2.0]non-1-(7)-ene 103.

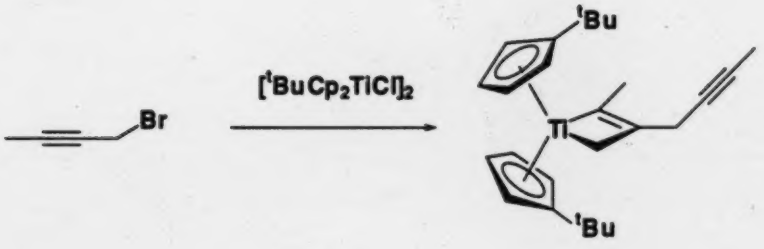


92 103

In the drybox, to a solution of $[^t BuCp_2TiCl]_2$ (16.3 mg, 0.025 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol, 3 equiv) at -35 °C. The resulting solution was treated with a solution of 1,8-dibromo-oct-2-yne **92** (13.4 mg, 0.05 mmol) in dry THF (1 mL) at -35 °C. The reaction mixture was maintained at room temperature for 1 h and then heated at 60°C for 5 h until the color of the solution changed to dark brown. The reaction mixture was cooled to room temperature and the volatiles removed *in vacuo*. The residue was triturated with pentane and then filtered through a plug of celite. Evaporation of the solvent from the filtrate under reduced pressure gave 8,8-bis(*tert*-butylcyclopentadienyl)titanabicyclo[5.2.0]non-1-(7)-ene **103** (15 mg, 75%) as a dark-red oil. Spectroscopic data for complex **103**: ^{1}H NMR (300 MHz, C_6D_6) δ 5.88 (narrow m, 2 H), 5.56 (narrow m, 2 H), 5.38 (narrow

m, 2 H), 5.34 (narrow m, 2 H), 3.31 (s, 2 H), 2.62 (br s, 2 H), 2.08 (m, 2 H), 1.53-1.70 (m, 4 H), 1.42-1.52 (m, 2 H), 1.15 (s, 18 H); $^{13}C\{^{1}H\}$ NMR (75 MHz, C_6D_6) δ 217.2, 139.0, 109.9, 109.4, 109.1, 106.9, 97.6, 79.4, 38.1, 33.4, 32.7, 31.7, 28.9, 26.8, 22.7; HRMS calcd. *m/z* for $C_{26}H_{38}Ti$ 398.2453, found 398.2451.

1,1-Bis(*tert*-butylcyclopentadienyl)-3-(2-butynyl)-2-methyltitanacyclobutene 104.

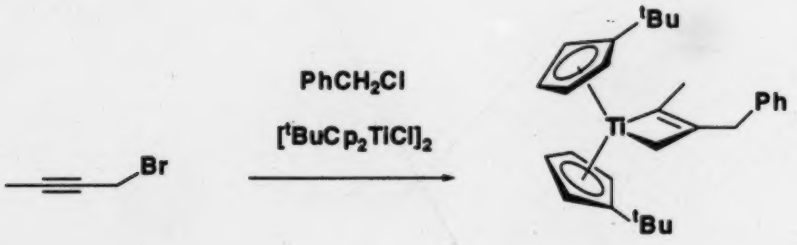


104

In the drybox, to a solution of $[^{t}BuCp_2TiCl]_2$ (32.6 mg, 0.05 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 3 mL, 0.3 mmol, 3 equiv) at -35 °C. The resultant solution was treated with a solution of 2-butynyl bromide (26.6 mg, 0.2 mmol, 2 equiv) in THF (1mL) at -35 °C. After shaking occasionally at -35 °C for 0.5 h, the solution was warmed to room temperature, during which time the color changed from dark blue to dark red. The reaction mixture was maintained at room temperature for 1 h, after which the volatiles were removed *in vacuo* and the residue was triturated with pentane and filtered through a plug of celite. Evaporation of the filtrate under reduced pressure gave 1,1-bis(*tert*-butylcyclopentadienyl)-3-(2-butynyl)-2-methyltitanacyclobutene **104** (32.8 mg, 83%) as a dark-red oil. The complex is stable for approximately 6 h in solution at room temperature, but decomposes slowly on prolonged

storage, even at -35 °C. Spectroscopic data for the complex **104:** ^{1}H NMR (360 MHz, C_6D_6) δ 5.85 (m, 2 H), 5.68 (m, 2 H), 5.56 (m, 2 H), 5.35 (m, 2 H), 3.36 (s, 2 H), 2.93 (m, 2 H), 2.14 (s, 3 H), 1.65 (s, 3 H), 1.13 (s, 18 H); ^{13}C {^{1}H} NMR (75 MHz, C_6D_6) δ 209.2, 139.9, 110.1, 109.6, 109.6, 107.6, 93.9, 77.8, 72.3, 68.5, 32.8, 31.7, 25.5, 19.6, 14.2; HRMS calcd. *m/z* for $C_{26}H_{36}Ti$ 396.2296, found 396.2301.

1,1-bis(*tert*-butylcyclopentadienyl)-3-benzyl-2-methyltitanacyclobutene 105.

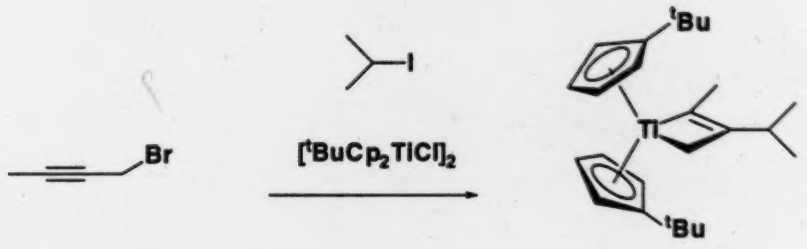


105

In the drybox, to a solution of $[^tBuCp_2TiCl]_2$ (32.6 mg, 0.05 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 3 mL, 0.3 mmol, 3 equiv) at -35 °C. The resulting solution was treated with a solution of 2-butynyl bromide (13.3 mg, 0.1 mmol, 1 equiv) and benzyl chloride (12.6 mg, 0.1 mmol, 1 equiv) in THF (1.5 mL) at -35 °C. After shaking occasionally for 0.5 h at -35 °C, the solution was warmed to room temperature, during which time the color changed gradually from dark blue to dark red. The reaction mixture was maintained at room temperature for 2 h, at which time the solution turned dark brown. The volatiles were removed *in vacuo* and the residue was triturated with pentane and filtered through a plug of celite. Evaporation of the solvent under reduced pressure gave 1,1-bis(*tert*-butylcyclopentadienyl)-3-benzyl-2-

methyltitanacyclobutene **105** (26.5 mg, 61%) as a dark-red oil. Spectroscopic data for the complex **105**: ^{1}H NMR (360 MHz, C_6D_6) δ 7.19–7.23 (m, 3 H), 6.96–7.13 (m, obscured by C_6D_6), 5.79 (m, 2 H), 5.52 (m, 2 H), 5.34 (m, 2 H), 5.27 (m, 2 H) 3.30 (s, 2 H), 3.03 (m, 2 H), 2.29 (m, 3 H), 1.07 (s, 18 H); ^{13}C {^{1}H} NMR (75 MHz, C_6D_6) δ 207.9, 141.1,. 139.5, 129.5, 128.7, 128.5, 126.1, 125.8, 110.3, 109.7, 109.5, 107.3, 95.9, 72.4, 35.6, 32.7, 31.6, 22.7; HRMS calcd. *m/z* for $C_{29}H_{38}Ti$ 434.2453, found 434.2455.

1,1-Bis(*tert*-butylcyclopentadienyl)-3-isopropyl-2-methyltitanacyclobutene 106.



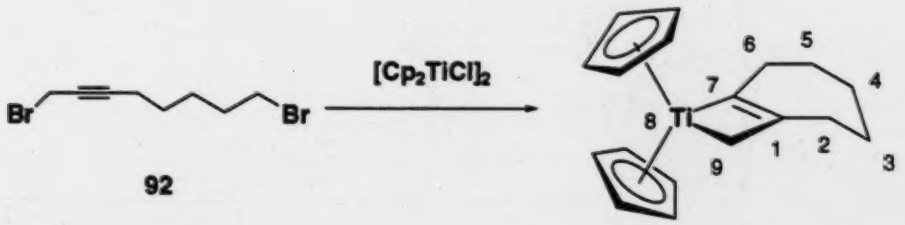
106

In the drybox, to a solution of $[^tBuCp_2TiCl]_2$ (32.6 mg, 0.05 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 3 mL, 0.3 mmol, 3 equiv) at -35 °C. The resulting solution was then treated with a solution of 2-butynyl bromide (13.3 mg, 0.1 mmol, 1 equiv) at -35 °C. The reaction mixture was shaken at -35 °C for 10 min, after which a solution of isopropyl iodide (17 mg, 0.1 mmol, 1 equiv) in THF (1.0 mL) was added at -35 °C. The resulting solution was warmed to room temperature, during which time the color changed gradually from dark blue to dark red. The reaction mixture was maintained at room temperature for 12 h (overnight) until the solution turned

dark brown. The volatiles were removed *in vacuo* and the residue was triturated with pentane and filtered through a plug of celite. Evaporation of the solvents under reduced pressure gave 1,1-bis(*tert*-butylcyclopentadienyl)-3-isopropyl-2-methyltitanacyclobutene **106** (24 mg, 62%) as a dark-red oil. Spectroscopic data for complex **106**: ^{1}H NMR (360 MHz, C_6D_6) δ 5.84 (q, J_{obs} = 1.6 Hz, 2 H, ^{t}BuC$_5$H$_4$), 5.58 (q, J_{obs} = 1.6 Hz, 2 H, ^{t}BuC$_5$H$_4$), 5.38 (q, J_{obs} = 1.6 Hz, 2 H, ^{t}BuC$_5$H$_4$), 5.34 (narrow m, 2 H, ^{t}BuC$_5$H$_4$), 3.08 (q, J_{obs} = 1.6 Hz, 2 H, H$_4$), 2.79 (septet, J = 6.8 Hz, 1 H, (CH$_3$)$_2$CH-), 2.16 (t, J = 1.6 Hz, 3H, -CH$_3$), 1.15 (s, 18 H, ^{t}BuC$_5$H$_4$), 0.96 (d, J = 6.8 Hz, 6 H, (CH$_3$)$_2$CH-); ^{13}C {^{1}H} NMR (75 MHz, C_6D_6) δ 208.6, 139.2, 110.3, 109.8, 109.6, 107.2, 99.5, 66.1, 32.7, 31.7, 25.4, 22.0, 20.7, 20.7; HRMS calcd. *m/z* for $C_{25}H_{38}Ti$ 386.2453, found 386.2454.

b. The use of the cyclopentadienyl template for titanacyclobutene formation.

8,8-Bis(cyclopentadienyl)titanabicyclo[5.2.0]non-1-(7)-ene 107 from 92.



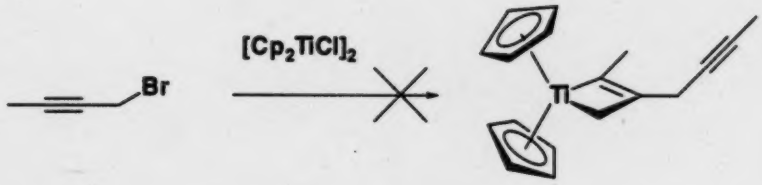
92 **107**

In the drybox, to a solution of $[Cp_2TiCl]_2$ (21.3 mg, 0.05 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 3 mL, 0.3 mmol, 3 equiv) at -35 °C.

The resulting dark-blue solution was treated with a solution of 1,8-dibromo-oct-2-yne **92** (26.8 mg, 0.1 mmol) in dry THF (1 mL) at -35 °C. The reaction mixture was allowed to warmed to room temperature. After 0.5 h at room temperature, the solution was transferred into a glass bomb and heated at 60°C for 7 h, until the color of the solution changed to dark brown. When the reaction mixture was cooled to room temperature, the volatiles were removed *in vacuo* and the residue was triturated with pentane. The combined pentane extracts were filtered through a plug of celite. Evaporation of solvent from the filtrate under reduced pressure gave 8,8-bis(cyclopentadienyl)titanabicyclo[5.2.0]non-1-(7)-ene **107** (20.1 mg, 72%) as a dark-red oil. For large scale preparation, the following method can be used to purify the product: the final pentane solution is concentrated to dryness and the residue is cooled at -35 °C for about 0.5 h. The cooled residue is redissolved in a minimum of pentane, leaving some impurities undissolved. After filtration, a product of greater purity can be obtained. Spectroscopic data for complex **107:** ^{1}H NMR (300 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, INAPT, and COSY spectra) δ 5.51 (s, 10 H, $C_5\underline{H}_5$), 3.32 (s, 2 H, H_9), 2.52 (m, 2 H, H_6), 1.99 (m, 2 H, H_2), 1.59 (m, 2 H, H_4),1.50 (m, 2 H, H_5), 1.40 (m, 2 H, H_3); ^{1}H-^{1}H GCOSY (300 MHz, C_6D_6, each correlation listed only once) δ 3.32 (H_9) ↔ 2.52 (H_6), 2.52 (H_6) ↔ 1.50 (H_5), 1.99 (H_2) ↔1.40 (H_3); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, INAPT, and COSY spectra) δ 219.9 (C_7), 110.0 ($\underline{C}_5H_5$), 92.7 (C_1), 82.8 (C_9), 37.6 (C_6) 32.6 (C_2), 31.6 (C_4),28.6 (C_5), 27.0 (C_3); INAPT (75 MHz, C_6D_6) irradiate δ = 3.32 (H_9), two carbon signals appear: δ 219.9 (C_7), 32.6 (C_2); HMQC (300 MHz, coupled, C_6D_6) δ 82.8 (C_9) ↔ δ 3.31 ($J_{C\text{-}H}$ = 137.6 Hz, H_9); δ 37.6 (C_6) ↔ δ 2.51 ($J_{C\text{-}H}$ =118.8 Hz, H_6); δ 32.6 (C_2) ↔ δ 1.99 ($J_{C\text{-}H}$ = 125.1 Hz, H_2); δ 31.6 (C_4) ↔ δ 1.59 ($J_{C\text{-}H}$ 112.6 Hz, H_4); 28.6 (C_5) ↔ δ 1.50 ($J_{C\text{-}H}$ = 131.3 Hz, H_5); δ 27.0 (C_3) ↔ δ 1.40 ($J_{C\text{-}H}$ =118.8 Hz, H_3); 110.0 ($\underline{C}_5H_5$) ↔ δ 5.51 ($J_{C\text{-}H}$ = 113.8 Hz, $C_5\underline{H}_5$); HMBC (300 MHz, C_6D_6, selected data only) δ 3.32 (H_9) ↔ δ 219.9 (C_7), 92.7 (C_1), 32.6 (C_2); δ1.99 (H_2) ↔ δ 219.9 (C_7), 92.7 (C_1), 82.8

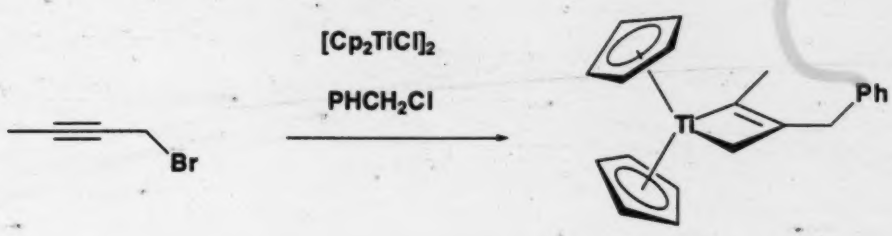
(C_9, weak), 31.6 (C_4), 27.0 (C_3); δ 1.59 (H_4) ↔ δ 28.6 (C_5) ; δ 1.50 (H_5) ↔ δ 219.9 (C_7), 37.6 (C_6, weak), 31.6 (C_4), 27.0 (C_3); δ 1.40 (H_3) ↔ δ 92.7 (C_1, weak), 31.6 (C_4), 28.6 (C_5); HRMS calcd. *m/z* for $C_{18}H_{22}Ti$ 286.1201, found 286.1200 .

Attempted to synthesis 1,1-Bis(cyclopentadienyl)-3-(2-butynyl)-2-methyltitanacyclobutene.



To a cold (-78°C) solution of $[Cp_2TiCl]_2$ (21.3 mg, 0.05 mmol) and SmI_2 (0.1 M in THF, 3 mL, 0.3 mmol, 3 equiv) in dry THF (2 mL) was added a solution of 2-butynyl bromide (26.6 mg, 0.2 mmol, 2 equiv) in THF (1mL) at -78 °C. The cooling bath was removed and the mixture was allowed to warmed slowly to room temperature. The resulting reaction mixture was stirred at room temperature for 20 h, during which time the colour of the solution changed from blue to brown. The solvent was evaporated *in vacuo* and the residue was triturated with pentane. The combined extracts were filtered through a short column of celite followed by concentration to give a dark–brown residue. The ^1H NMR spectrum showed that the residue is a decomposed mixture and no desired compound was observed.

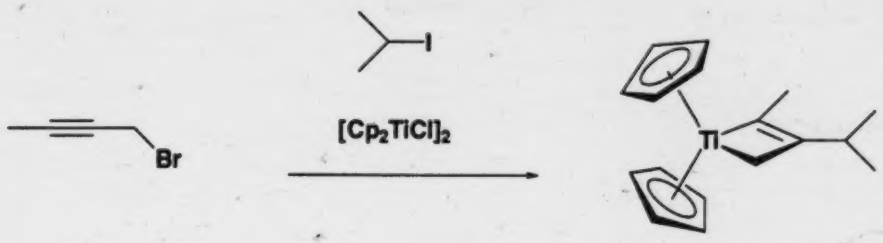
1,1-Bis(cyclopentadienyl)-3-benzyl-2-methyltitanacyclobutene 108.



108

In the drybox, to a solution of $[Cp_2TiCl]_2$ (21.3 mg, 0.05 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 3 mL, 0.3 mmol, 3 equiv) at -35 °C. The resulting blue solution was treated with a solution of 2-butynyl bromide (13.3 mg, 0.1 mmol, 1 equiv) and benzyl chloride (12.6 mg, 0.1 mmol, 1 equiv) in THF (1.5 mL) at -35 °C. The reaction mixture was warmed to room temperature. Over a few minutes at room temperature, the solution color changed gradually from dark blue to dark red. The reaction mixture was maintained at room temperature for 20 min, until the solution turned dark brown. The volatiles were removed *in vacuo* and the residue was triturated with pentane and filtered through a plug of celite. Evaporation of solvent from the filtrate under reduced pressure gave 1,1-bis(cyclopentadienyl)-3-benzyl-2-methyltitanacyclobutene **108** (21.9 mg, 68%) as a dark-red oil. Spectroscopic data for the complex **108:** ^1H NMR (360 MHz, C_6D_6) δ 7.17–7.23 (m, 2 H, Ph), 7.05–7.11 (m, 3 H, Ph), 5.44 (s, 10 H, C_5H_5) 3.23 (s, 2 H, $PhCH_2$), 3.05 (q, J = 1.6 Hz, 2 H, H_4), 2.22 (t, , J = 1.6 Hz, 3 H, CH_3); ^{13}C {^1H} NMR (75 MHz, C_6D_6) δ211.1, 141.0, 129.4, 126.3, 125.8, 121.8, 115.2, 110.3, 90.9, 75.7, 34.7, 21.9; HRMS calcd. *m/z* for $C_{21}H_{22}Ti$ 322.1201, found 322.1199.

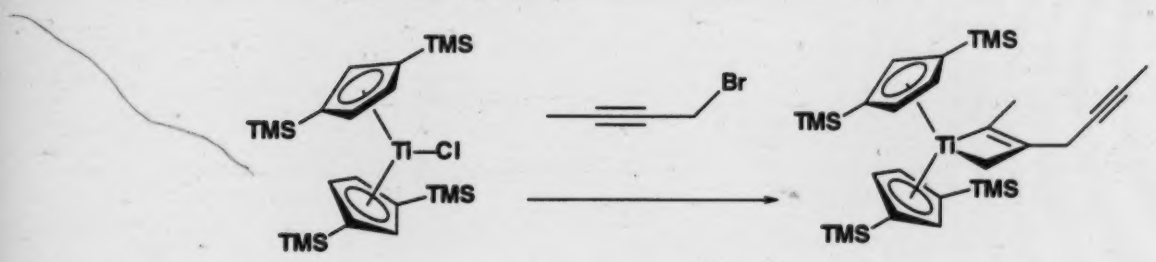
1,1-Bis(cyclopentadienyl)-3-isopropyl-2-methyltitanacyclobutene 109.



109

In the drybox, to a solution of $[Cp_2TiCl]_2$ (21.3 mg, 0.05 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 3 mL, 0.3 mmol, 3 equiv) at -35 °C. The resulting blue solution was treated with a solution of 2-butynyl bromide (13.3 mg, 0.1 mmol, 1 equiv) at -35 °C. The reaction mixture was shaken occasionally and maintained at -35 °C (in drybox freezer) for 10 min, after which isopropyl iodide (17 mg, 0.1 mmol, 1 equiv) in THF (1.0 mL) was added at -35 °C. The solution was warmed to room temperature and maintained there for 18 h (overnight), during which time the solution turned dark brown. The volatiles were removed *in vacuo* and the residue was triturated with pentane and filtered through a plug of celite. Evaporation of the solvent from the filtrate under reduced pressure gave 1,1-bis(cyclopentadienyl)-3-isopropyl-2-methyltitanacyclobutene **109** (21 mg, 77%) as a dark-red oil. Spectroscopic data for the **109**: ^{1}H NMR (360 MHz, C_6D_6) δ 5.49 (s, 10 H, $C_5\underline{H}_5$), 3.10 (q, J_{obs} = 1.6 Hz, 2 H, H_4), 2.74 (septet, J = 6.8 Hz, 1 H, $(CH_3)_2C\underline{H}$-), 2.10 (t, J = 1.6 Hz, 3H, -CH_3), 0.89 (d, J = 6.8 Hz, 6 H, $(\underline{C}H_3)_2CH$-); ^{13}C {^{1}H} NMR (75 MHz, C_6D_6) 211.8, 110.3, 94.2, 69.0, 24.8, 21.3, 20.8, 20.8; HRMS calcd. *m/z* for $C_{17}H_{22}Ti$ 274.1201, found 274.1197.

1,1-Bis[1,3-bis(trimethylsilyl)cyclopentadienyl]-3-(2-butynyl)-2-methyltitanacyclobutene 111.

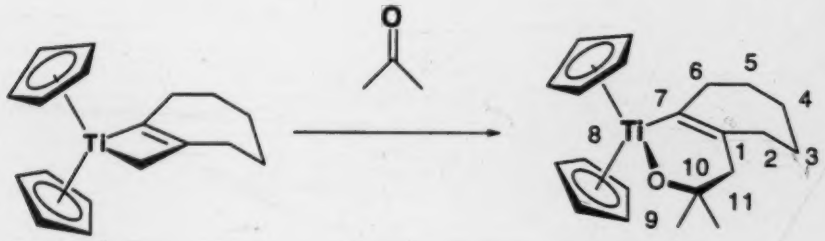


110 **111**

In the drybox, to a solution of silylated titanocene chloride **110** (25.1 mg, 0.05 mmol) in THF (1mL) at -35 °C was added a solution of SmI_2 (0.1 M in THF, 1.5 mL, 0.15 mmol, 3 equiv) at -35 °C. The resulting mixture was treated with a solution of 2-butynyl bromide (13.3 mg, 0.1mmol, 2 equiv) in THF (1mL) at -35 °C. The reaction mixture was warmed to room temperature, during which time the color changed gradually from dark blue to dark red. The reaction solution was maintained at room temperature for 1 h until the solution turned dark brown. The volatiles were removed *in vacuo* and the residue were triturated with pentane and filtered through a plug of celite. Evaporation of solvent from the filtrate under reduced pressure gave 1,1-bis[1,3-bis (trimethylsilyl)cyclopentadienyl]-3-(2-butynyl)-2-methyltitanacyclobutene **111** (26 mg, 91%) as a dark-red oil. Spectroscopic data for complex **111:** ^{1}H NMR (360 MHz, C_6D_6) δ 6.43 (s, 2 H), 5.95 (s, 2 H), 5.88 (s, 2 H), 3.48 (s, 2 H), 2.87 (s, 2 H), 2.20 (s, 3 H), 1.66 (s, 3 H), 0.20 (s, 36 H); ^{13}C {^{1}H} NMR (75 MHz, C_6D_6) δ 211.5, 127.3, 125.6, 117.7, 117.3, 91.4, 77.9, 76.3, 74.1, 23.9, 19.4, 3.6, 0.4; HRMS calcd. *m/z* for $C_{30}H_{52}SiTi$ 572.2626, found 572.2631.

c. Functionallization of titanacyclobutene complexes

8,8-Bis(cyclopentadienyl)titana-9-oxa-10,10-dimethylbicyclo[5.4.0]undec-1-(7)-ene 122.

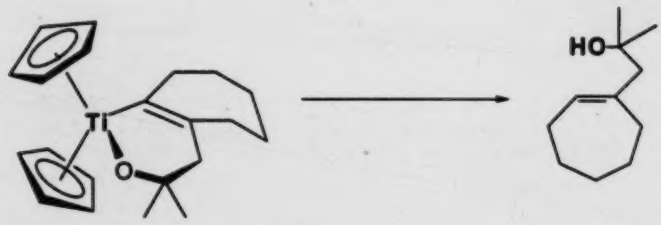


107 **122**

In the drybox, to a solution of 8,8-bis(cyclopentadienyl)titanabicyclo[5.2.0]non-1-(7)-ene **107** (28.6 mg, 0.1 mmol) in benzene-d_6 (1.5 mL) was added a solution of anhydrous acetone (29 mg, 0.5 mmol, 5 equiv) in benzene (1 mL). The resulting dark red solution was placed in a glass bomb and heated at 60°C for 4 days. The resulting orange red solution was cooled to room temperature, filtered through a short column of celite, and concentrated to afford 8,8-bis(cyclopentadienyl)titana-9-oxa-10,10-dimethyl-bicyclo[5.4.0]undec-1-(7)-ene **122** as an orange-red oil (24.8 mg, 72%). Spectroscopic data for insertion product **122**: ^{1}H NMR (300 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, and COSY spectra) δ 5.83 (s, 10 H, $C_5\underline{H}_5$), 2.29 (s, 2 H, H_{11}), 2.22 (m, 2 H, H_2), 2.02 (m, 2 H, H_6), 1.80 (m, 2 H, H_4) 1.62 (m, 2 H, H_5), 1.50 (m, 2 H, H_3), 1.10 (s, 6H, CH_3); ^{1}H-^{1}H GCOSY (300 MHz, C_6D_6, each correlation listed only once) δ 2.29 (H_{11}) ↔ 2.02 (H_6); 2.22 (H_2) ↔ 1.50 (H_3), 2.02 (H_6) ↔1.62 (H_5); 1.80 (H_4)↔ 1.62 (H_5), 1.50 (H_3); ^{13}C {^{1}H} NMR (75 MHz, C_6D_6, assignments confirmed by HMQC, HMBC, and COSY spectra) δ 191.6 (C_7), 133.5 (C_1), 112.3 ($\underline{C}_5H_5$), 86.8

(C_{10}), 60.9 (C_{11}), 39.2 (C_6) 37.4 (C_2), 33.0 (C_4), 29.2 (C_3), 28.0 (CH_3), 26.8 (C_5); HMQC (300 MHz, coupled, C_6D_6); 112.3 ($\underline{C}_5H_5$) ↔ δ 5.83 ($J_{C\text{-}H}$ = 170.0 Hz, $C_5\underline{H}_5$); δ 60.9 (C_{11}) ↔ δ 2.29 ($J_{C\text{-}H}$ =125.1 Hz, H_{11}); δ 39.2 (C_6) ↔ δ 2.02 ($J_{C\text{-}H}$ = 120.9 Hz, H_6); δ 37.4 (C_2) ↔ δ 2.22 ($J_{C\text{-}H}$ = 125.1 Hz, H_2); δ 33.0 (C_4) ↔ δ 1.80 ($J_{C\text{-}H}$ = 158 Hz, H_4); 29.2 (C_3) ↔ δ 1.50 ($J_{C\text{-}H}$ = 141.8 Hz, H_3); 28.0 ($\underline{C}H_3$) ↔ δ 1.10 ($J_{C\text{-}H}$ = 125.1 Hz, $C\underline{H}_3$); δ 26.8 (C_5) ↔ δ 1.62 ($J_{C\text{-}H}$ 150.1 Hz, H_5); HMBC (300 MHz, C_6D_6, selected data only) δ 2.29 (H_{11}) ↔ δ 191.5 (C_7), 133.5 (C_1), 86.8 (C_{10}); 39.1 (C_6), 28.0 ($\underline{C}H_3$); δ 2.22 (H_2) ↔ δ 191.5 (C_7), 133.5 (C_1), 60.9 (C_{11}, weak), 33.0 (C_4), 26.8 (C_5, weak); δ 2.02 (H_6) ↔ δ 191.5 (C_7), 133.5 (C_1), 33.0 (C_4, weak); δ 1.80 (H_4) ↔ δ 39.2 (C_6) ; δ 1.50 (H_3) ↔ δ 133.5 (C_1); δ 1.10 ($C\underline{H}_3$) ↔ δ 86.8 (C_{10}), 60.9 (C_{11}), 28.0 ($\underline{C}H_3$); HRMS calcd. *m/z* for $C_{21}H_{28}TiO$ 344.1619, found 344.1628 .

1-cyclohept-1-enyl-2-methylpropane-2-ol 123.

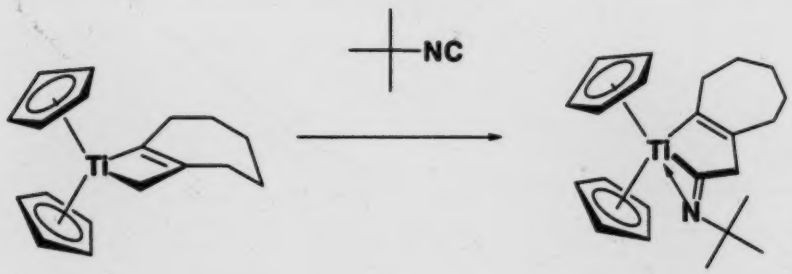


122 **123**

In the drybox, a solution of 8,8-bis(cyclopentadienyl)titana-9-oxa-10,10-dimethylbicyclo[5.4.0]undec-1-(7)-ene **122** (34.4 mg, 0.10 mmol) in Et_2O (3 ml) was placed in a glass bomb. The reaction vessel was sealed and taken out of the drybox. The side arm of the bomb was connected to the Schlenk line. After several applications of vacuum and back–filling with nitrogen, the stopcock was replaced by a rubber septum

under a strong nitrogen flush. The bomb was cooled to 0°C in a ice-water bath and dry HCl gas was introduced into the solution via a long syringe needle. After 5 minutes of bulling with HCl, the reaction mixture was warmed to room temperature, diluted with Et_2O (2 mL), and filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by flash silica gel chromotography, eluting with a solvent mixture of ethyl acetate in hexane (v/v, 1:3) to afford 1-cyclohept-1-enyl-2-methylpropane-2-ol **123** (14 mg, 83%) as a yellow oil. This material was spectroscopically identical to the literature reported compound.[117] Additional spectroscopic data for compound **123:** FTIR (KCl) 3418 (br m), 2967 (s), 2921 (s), 2849 (s), 1661 (w), 1652 (w), 1447 (w), 1372 (w), 1276 (w), 1260 (w), 1217 (w), 1142 (w), 966 (w), 906 (w), 850 (w), 753 (w), 702 (w), 667 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.62 (t, J = 6.8 Hz, 1 H), 2.20–2.23 (m, 2 H), 2.17 (s, 2 H), 2.10–2.15 (m, 2 H) , 1.71-1.80 (m, 2 H), 1.60–1.68 (br s, 2 H), 1.45-1.54 (m, 2 H), 1.20 (s, 6 H) ; ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 141.9, 131.6, 70.5, 53.7, 35.3, 32.7, 29.7, 29.7, 28.7, 27.2, 26.8; HRMS calcd. *m/z* for $C_{11}H_{20}O$ 168.1514 found 168.1508.

tert-Butyl isocyanide insertion product 124 from 8,8-Bis(cyclopentadienyl)titanabicyclo[5.2.0]non-1-(7)-ene 107.



107 **124**

In the drybox, to a solution of 8,8-Bis(cyclopentadienyl)titana-bicyclo[5.2.0]non-1-(7)-ene **107** (22 mg, 0.077 mmol) in dry toluene (1.5 mL) at -35°C was added a solution of tert-butyl isocyanide (6.4 mg, 0.077 mmol, 1 equiv) in toluene at -35°C. The resulting solution was warmed slowly to room temperature and stirred for 6 h. The solvent was removed *in vacuo* and the residue was dried on the high vacuum line (10^{-6} torr) to remove the toluene residue. The insertion product **124** was obtained (quantitative). Spectroscopic data for complex **124:** ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.29 (s, 10 H), 3.64 (s, 2 H), 2.50 (m, 2 H), 2.44 (m, 2 H) , 1.91 (m, 2 H), 1.79 (m, 2 H), 1.68 (m, 2 H), 0.92 (s, 9 H) ; ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 225.6, 190.5, 143.0, 105.0, 59.3, 53.6, 41.9, 33.7, 31.9, 29.7, 29.3, 27.9; HRMS calcd. *m/z* for $C_{13}H_{21}N$ (M^+-Cp_2Ti)191.1674, $C_{10}H_{10}Ti$ (Cp_2Ti) 178.0262, found $C_{13}H_{21}N$ (M^+-Cp_2Ti) 191.1688, $C_{10}H_{10}Ti$ (Cp_2Ti) 178.0263.

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